JAVELIN MEDLEY

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

STATISTICAL ANALYSIS PLAN – B9991004

Compounds:	MSB0010718C PF-05082566 PF-04518600 PD 0360324 CMP-001
Compound Name:	Avelumab (MSB0010718C) Utomilumab (PF-05082566)
Version:	Version 6
Date:	22-Feb-2022

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B9991004 is based on the protocol amendment 8 dated 27-Feb-2019.

Table 1. Summary of Major Changes in SAP Amendments

Version	Version Date	Summary of Changes
6	22-Feb-2022	Section 2 "Introduction" - this section was modified to indicate that the primary analysis will occur after last subject last visit across all tumor types and combinations. Section 6.4 "Subset Analyses" - relapse and resistant categories for prior checkpoint inhibitor status are now combined. Section 6.2.6.1 "Time to and Duration of ADA" - removed text regarding assessments after discontinuation for censoring. Section 6.2.2.6 "Overall Survival" - added the following text "OS analysis will be conducted for patients up to LSLV of the study". Minor editorial and consistency changes throughout the document.
5	17-Dec-2020	Section 3.4.2 "Baseline characteristics" - removed "physical measurements". Section 6.2.2.3 "Duration of response" - removed listing for DR. Section 6.2.2.5 "Progression-free survival" - removed time of follow-up for PFS. Section 6.2.2.6 "Overall survival" - removed time of follow-up for OS. Section 6.2.3 "Pharmacokinetic endpoints" - removed linear-linear and log-linear PK plots. Section 6.2.6.3 "Analysis of PK by immunogenicity status"- removed data listing for immunogenicity and relevant PK and safety data; removed "safety" from header. Section 6.2.6.3 "Analysis of PK by immunogenicity status" - removed safety and immunogenicity summaries; removed log-linear plots. Section 6.4 "Subset Analyses" - combined subset of prior PD-1 and PD-L1 into PD-1/PD-L1; added in PD-L1 subset analysis and CD8 descriptive analysis by OR. Section 6.5.1 "Baseline summaries" - updated listing to Prior anti-cancer drug therapies. Section 6.5.1.1 "Demographic characteristics" - removed reference to "physical measurements", and to height, weight, BMI and BSA. Section 6.5.4 "Concomitant medications and non-drug treatments" - removed prior medication summaries and listings; removed anti- cancer treatment listings. Section 6.6.1.1 "All adverse events" - removed summary of TEAE leading to interruption of individual study drugs and included any study drug; Removed redundant summary for TEAE; removed summaries for TEAEs by SOC and PT related to each study drug; added TEAEs related to any study drug by SOC and PT and grade. Section 6.6.1.2 "Adverse events leading to interruption of study treatment" - removed summary of TEAE leading to interruption of CMP. Section 6.6.5.1 "Hematology and chemistry parameters" - removed summary of laboratory parameters by CTCAE grade table. Section 6.6.4 "Other significant adverse events" - removed summary of irAE (and IRR) leading to discontinuation of a study drugs (except Avelumab); removed summary of irAE (and IRR) by death and grade >=3. Section 6.6.5.2 "Other laboratory parameters" - removed listing of abnormal values for hematology, chemistry, urinalysis, and coagulation. Section 6.6.6 "Vital signs" - removed vital signs summaries.

		Section 6.6.7 “Electrocardiogram” - removed ECG listings and ECG summaries by timepoint. Table 15 “Case Definition for irAEs” - added in “Steps 3 and 4 will be checked concurrently. Step 5 will be checked if the criteria in Step 4 is met, irrespective of whether the Criteria in Step 3 is met”.
4	10-Jun-2019	Updated study objectives (Section 2.1), endpoints (Section 3.1, Section 3.3, Section 6.3), study design (Section 2.2), study treatments (Section 3.4.1), definition of DLT-evaluable set (Section 4.3.1), sample size (Section 5.1.1), decision rules (Section 5.1.2) and associated statistical considerations (Section 6 and subsections) as per revisions in Protocol Amendments 6 through 8. In addition, the following updates were made to the SAP. Sections 3.2.2 and 6.2.3 “Pharmacokinetic endpoints” – aligned content of Table 2 and associated analyses to the protocol-specified endpoints. Section 3.2.3 “Immunogenicity endpoints”, Section 4.3.4 “Immunogenicity analysis set”, Section 6.2.6 “Endpoints for immunogenicity data of avelumab and other study drugs” – deleted reference to neutralizing antibodies (nAb) since not specified in the protocol. Section 3.4.1 “Study drug, study treatment and baseline definitions” – added definition of baseline for immunogenicity analyses. Section 3.5 “Adverse Events” - the definition of Treatment-emergent adverse events (TEAEs) was modified to include all AEs with onset date during the on-treatment period. Cytokine Release Syndrome was added as an AE of special interest for Combination F. Section 5.2.10 “Adequate baseline tumor assessment” - the criteria were updated to include only criteria that can be derived programmatically. Section 5.3.3.1 “Date of last contact” – added withdrawal of consent date in the derivation of date of last contact. Section 5.3.3.4 “Date of start of new anti-cancer therapy” – revised to include additional details of imputation rules for incomplete dates for start date of new anti-cancer therapy. Section 6.2.2.3 “Duration of response” – added details regarding censoring for duration of response since “no adequate baseline assessment” which is used in censoring for PFS analyses is not applicable to analyses of duration of response for patients with objective response. Updated the time points for derivation of DR rates to be aligned with the schedule of tumor assessments. Section 6.2.2.5 “Progression-free survival” - updated the time points for derivation of PFS rates to be aligned with the schedule of tumor assessments; added further details for summary of time of follow-up for PFS. Section 6.2.2.6 “Overall survival” – updated the time points for derivation of OS rates; added further details for summary of time of follow-up for OS. Section 6.2.5 “Biomarker endpoints” – simplified analyses to include only descriptive summaries. Section 6.2.6 “Endpoints for immunogenicity data of avelumab and other study drugs”- added details for the analyses of ADA. Section 6.5.1.3 “Disease characteristics” – simplified summaries for smoking history. Section 6.5.1.4 “Prior anti-cancer therapies” – aligned with data collected in eCRF. Section 6.5.2.1 “Patient disposition” – deleted references to randomization stratification factors since not applicable to the study. Section 6.5.3 “Study treatment compliance and exposure” – added derivations for CMP-001 as per Protocol Amendment 8; deleted by-cycle summaries; deleted summaries for dose omissions, dose delays, infusion rate reductions and

		infusion interruptions since such changes are captured in the overall derivation of relative dose intensity. Section 6.6.1 "Adverse events" and subsections – updated definition of treatment-emergent adverse event; added summaries of AEs leading to interruption of study drug; added summaries for cykotine release syndrome (Combination F only); given the nature of immune-related AEs (irAEs) and infusion related reactions (IRRs), removed the summaries of treatment-related irAEs and treatment-related IRRs; removed the requirement that all summaries by SOC and PT will be replicated by PT only. Section 6.6.2 "Death" – deleted references to primary reason for death since not collected in the eCRF. Section 6.6.5 "Laboratory data" and subsections –added summary for patients with newly occurring or worsening laboratory abnormities; updated lab parameters as per protocol; deleted summaries of laboratory data by time point since the data can adequately be characterized and interpreted based on CTCAE grade and shift tables to low, normal and high for parameters that are not graded per CTCAE. Section 6.6.7 "Electrocardiogram" – deleted QTcP since the number of patients enrolled in each cohort is small. Section for "Physical Examination" was removed as data not collected in the eCRF (abnormal findings are reported as AEs). Section 8 "References" – references updated. Appendix 1 "Immune-related Adverse Events" – updated the ATC codes for concomitant medications in Step 4 of the case definition for irAEs and added a statement regarding medical review if needed to refine the programmatic derivation. Minor editorial and consistency changes throughout the document.
3	06-Dec-2016	Updated objectives, endpoints, study design, sample size and other statistical considerations as per revisions in Protocol Amendment 5, namely as it pertains to the addition of the SCLC and 1L NSCLC cohorts in Phase 2 of Combination A, addition of Combinations C and D. Additional changes and updates described below. Section 2 "Introduction" – changed the cut-off date for the primary CSR from 12 to 18 months after last patient first treatment to allow for efficacy data to mature and to have longer follow-up for safety. Section 3.4.1 "Study drug, study treatment and baseline definitions" – added definition of end date of study treatment; referred to RR instead of heart rate in ECG baseline derivations since the CRF collects RR rather than heart rate. Start of new anti-cancer drug therapy and start of new anti-cancer therapy are added in Sections 5.2.5 and 5.2.6, respectively. Section 5.2.10 "Adequate baseline tumor assessment" and 5.2.11 "Adequate post-baseline tumor assessment" were added Section 5.3.3.4 "Date of start of new anti-cancer therapy" was added to provide details of imputation rules for incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery). Section 6.1.2.1 "Primary analysis" of OR by investigator assessment – added an additional reason for BOR of NE associated with inadequate or missing baseline assessment; included an additional reason for NE associated with death prior to first post-baseline tumor assessment; added definition of BOR of non-CR/non-PD for patients without measurable disease at baseline. Section 6.2.2.2 "Disease control" –corrected the definition of DC to include BOR of non-CR/non-PD to take into account patients without measurable disease at baseline.

		Section 6.2.2.5 “Progression-free survival”– provided more details and hierarchy associated with the derivation of reasons for censoring. Section 6.2.2.6 “Overall survival” – provided more details and hierarchy associated with the derivation of reasons for censoring. Section 6.3.1 “irRECIST endpoints” – added irNE as a category for irBOR and provided more details for outcome and event dates for irPFS and irDR as was done for PFS and DR. Section 6.4 “Subset Analyses” – added subcategories to prior checkpoint inhibitor status (now includes relapsed, refractory, resistant, naïve). Section 6.5.1.1 “Demographic characteristics” – added Middle East as another possible geographic region and changed the geographic region Australia to Australasia. Section 6.5.1.3 “Disease characteristics” – added time since diagnosis of local/regional recurrence of disease. Section 6.5.1.4 “Prior anti-cancer therapies” – clarified that prior anti-cancer therapies will be listed together with concomitant and follow-up therapies but with a flag to identify them as prior therapies. Removed the summary of prior anti-cancer drug therapies and radiotherapy due to the first-line setting of the study. Section 6.5.2.1 “Patient disposition” –clarified the summary descriptions to match the CRF data collection and descriptors Section 6.5.3 “Study treatment compliance and exposure” – provided details regarding cycle derivations Section 6.5.3.6 “Dose omissions” and Section 6.5.3.9 “Infusion interruptions” were added. Section 6.5.3.7 “Dose delays” – provided further derivation details. Section 6.5.3.8 “Infusion rate reductions” – added further derivation details. Section 6.5.4 “Concomitant medications and non-drug therapies” – non-drug treatments will be listed but not summarized Section 6.5.5 “Subsequent anti-cancer therapies” – deleted the summary of BOR across all anti-cancer drug therapies since not meaningful from a clinical standpoint. Section 6.6.1 “Adverse events” and subsections – corrected details associated with irAE and IRR based on FDA feedback. Section 6.6.5 “Laboratory data” and subsections –corrected the descriptor of the eDISH plot; changed the formula for corrected calcium to be expressed in SI units; clarified that the denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for the particular summary. Section 6.6.7 “Electrocardiogram” – clarified that the denominator to calculate percentages for each category is the number of patients evaluable for the particular summary. Deleted the summary for patients with ECG abnormalities based on morphology since collected in a free text field. Section 9 “Appendices” – added appendices with the irAE and IRR derivation rules; deleted the tabulation of cycle derivations since included with more details in the exposure section. Minor editorial and consistency changes throughout the document.
2	01-Apr-2016	Changed objectives, endpoints, and other statistical considerations as per revisions in Protocol Amendment 2 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. Analysis sets updated to include those for Combination B.

		Added statistical methods and decision rules for Combination B. Updated to include sample size determination for the TNBC cohort for Combination A and sample size determination for Combination B. Updated to include Combination B in efficacy analysis. Updated document throughout to include specific details for Combination B.
1	03-Sep-2015	Original SAP

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B9991004. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Statistical analyses will be performed using cleaned eCRF data as well as non-CRF data (ie, biopsy data from the central laboratory and pharmacokinetic (PK) data).

The primary analysis will occur after the last subject last visit (LSLV) has been achieved across all tumor types and combinations.

Additional analyses of the data may be performed for publication or regulatory reporting purposes.

Throughout this document 'start date' refers to date of randomization for randomized cohorts and first dose of study treatment for non-randomized cohorts.

2.1. Study 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 recommended Phase 2 dose(s) [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.

CCI [redacted]

- CCI [redacted]

- CCI [redacted]

2.2. Study Design

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). 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.

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 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 to evaluate efficacy and further evaluate safety of the selected dose from the Phase 1b part in prespecified patient populations.

2.2.1. Combination A

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

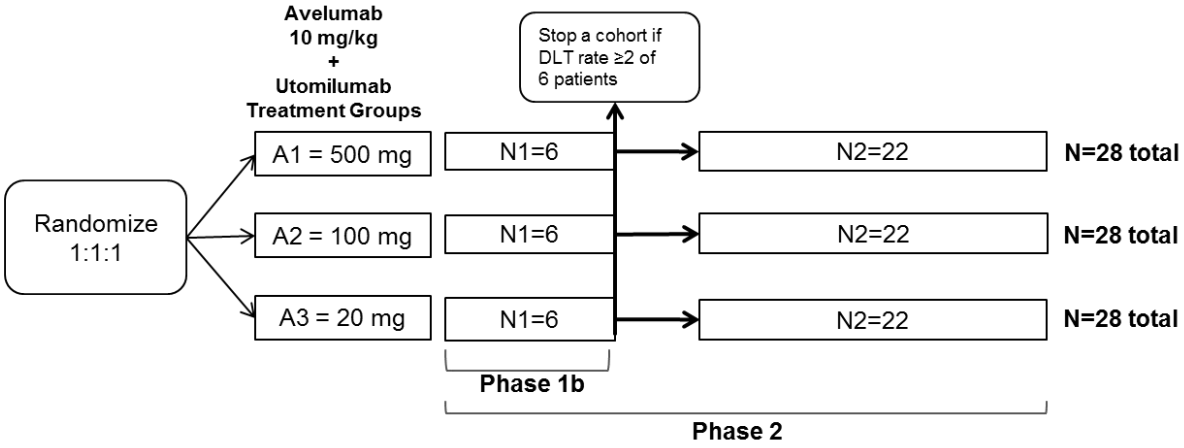
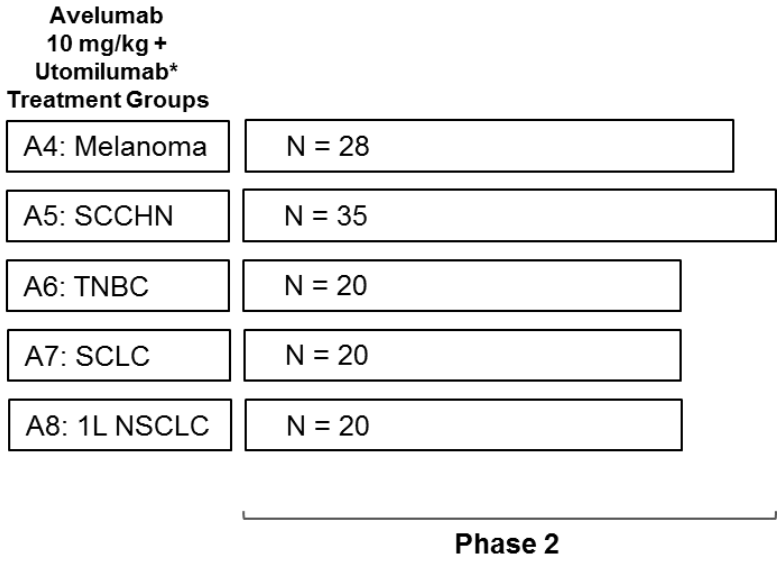
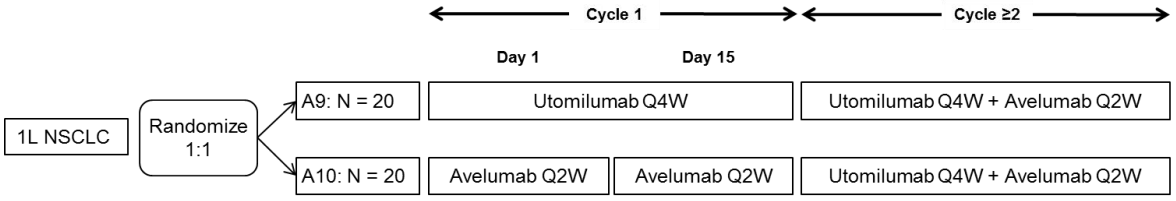


Figure 2. Combination A Phase 2 Study Design Schema - Melanoma (Cohort A4), SCCHN (Cohort A5), TNBC (Cohort A6), SCLC (Cohort A7), and First-Line NSCLC (Cohort A8)



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

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



Phase 1b lead-in

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 dose-limiting toxicity (DLT) is observed in at least 2 of 6 DLT-evaluable patients treated within a cohort, further evaluation of the cohort will be stopped. Patients treated in Phase 1b who are not considered DLT evaluable (as defined in Section 3.1) will be replaced for the assessment of the DLT rate in the cohort to which they were randomized.

Phase 2

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 for 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 advanced NSCLC (Cohort A8; N=20, up to 26 patients will be enrolled to achieve a minimum of 20 PD-L1-positive patients). Enrollment into Cohorts A7 and A8 may be staged based on activity observed during the Phase 1b part 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.

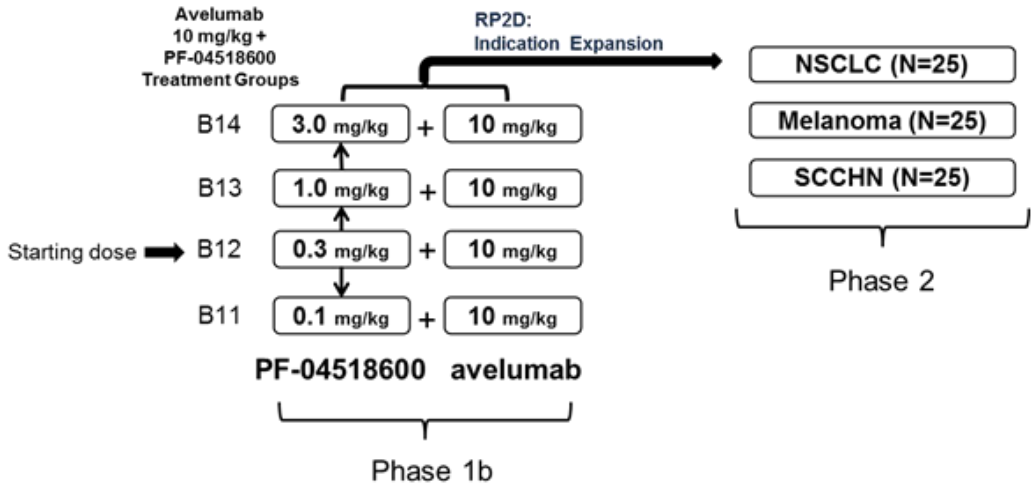
Sequenced (single agent administration for 1 cycle followed by combination therapy) administration of single agent avelumab or utomilumab for 1 cycle followed by administration of combination (avelumab plus utomilumab) will be evaluated in 2 additional cohorts. Both cohorts will enroll 20 patients each 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.

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.

2.2.2. Combination B

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



Phase 1b lead-in

In the Phase 1b part for Combination B, patients with locally advanced or metastatic solid tumors will be evaluated to identify the MTD or MAD of avelumab plus PF-04518600 using the modified toxicity probability index (mTPI) design as described in Section 5.1.2. Patients will receive PF-04518600 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 as described in Section 5.1.2. 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.

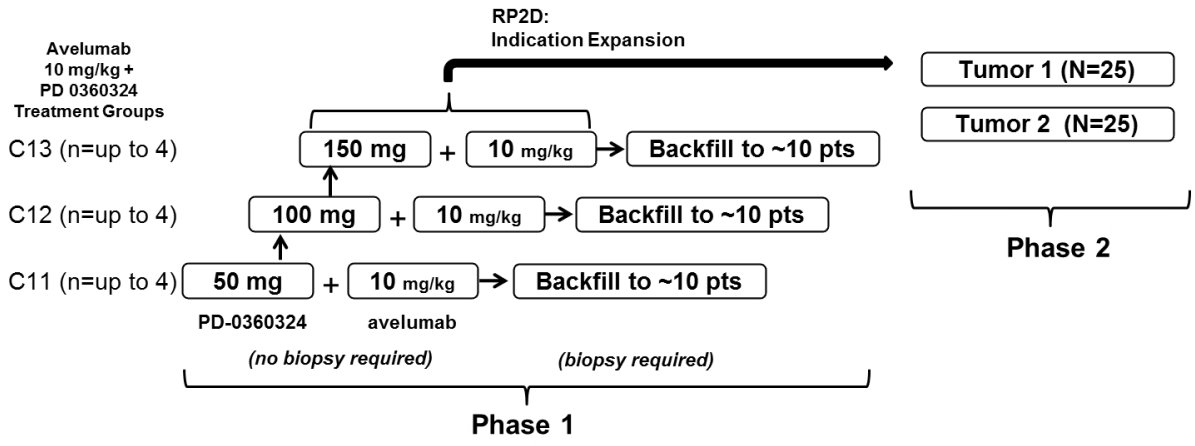
Phase 2

Once the Phase 1b part is completed and the MTD or MAD is determined, the Phase 2 part 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.

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.

2.2.3. Combination C

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



Phase 1b lead-in

In the Phase 1b lead-in for Combination C, patients with locally advanced or metastatic solid tumors will be evaluated to identify the MTD or MAD of avelumab plus PD 0360324 using

the mTPI design described in Section 5.1.2. Patients will receive PD 0360324 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. If at any point the mTPI requires a de-escalation, the next 3 patients will be enrolled at the lower dose level as described in Section 5.1.2. 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.

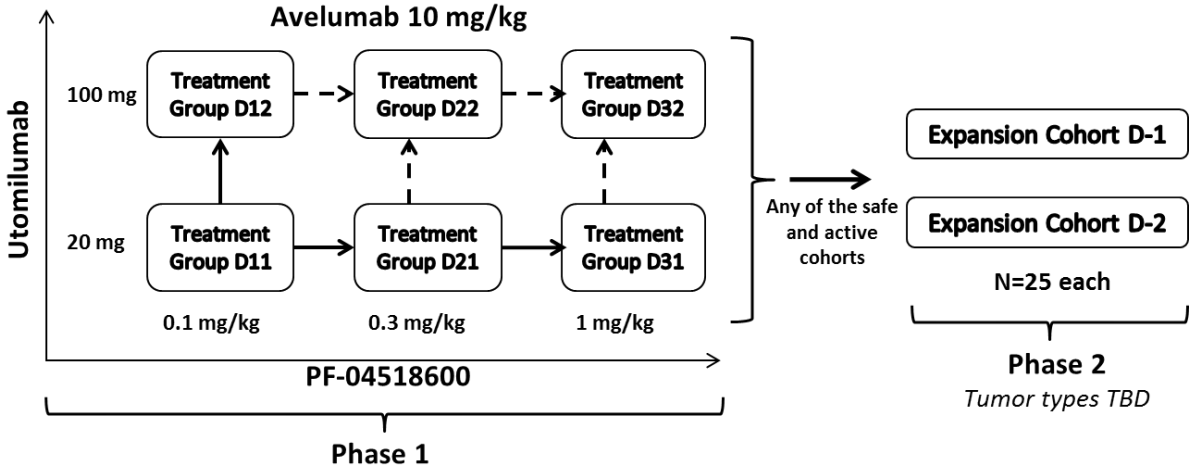
Phase 2

Once the Phase 1b is completed and the MTD or MAD is determined, the Phase 2 part 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.

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.

2.2.4. Combination D

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 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.

Phase 1b lead-in

In the Phase 1b part for Combination D, patients with locally advanced or metastatic solid tumors will be evaluated to identify the MTD or MAD of avelumab plus utomilumab plus PF-04518600 using the mTPI design described in Section 5.1.2. Patients will receive utomilumab plus PF-04518600 in combination with avelumab Q2W for 2 cycles (8 weeks) and will 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 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. If at any point the mTPI requires de-escalation, the next 3 patients will be enrolled at the lower dose level as described in Section 5.1.2. 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.

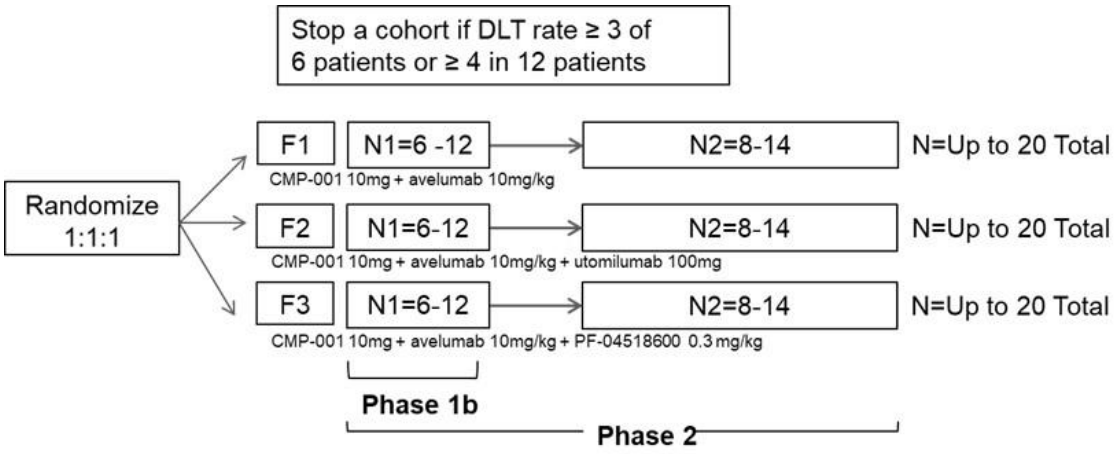
Phase 2

Once the Phase 1b lead-in is completed and the MTD or MAD is determined, the Phase 2 part 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.

Up to approximately 122 patients will be enrolled for Combination D treatment.

2.2.5. Combination F

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



Phase 1b lead-in and Phase 2

In the Phase 1b safety lead-in, 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 lead-in and evaluated for DLT during the first treatment cycle (4 weeks) as described in Section 5.1.1.

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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoints

- Phase 1b lead-in:
  - First 2 Cycles DLT(s) for Combinations A, B, C and D;
  - First Cycle DLT(s) for Combination F only.

  Severity of adverse events (AEs) will be graded according to Common Terminology Criteria for Adverse Events [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 $<0.5 \times 10^9/L$) 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 $<1.0 \times 10^9/L$, and Grade >3 infection);
  - Grade ≥3 thrombocytopenia (platelet count $<50,000 - 25,000/mm^3$ or $<50.0 – 25.0 \times 10^9/L$) with bleeding;
  - Grade 4 thrombocytopenia (platelet count $<25,000/mm^3$ or $<25.0 \times 10^9/L$);
  - 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.

- Phase 2: Confirmed objective response (OR), as assessed by the Investigator using RECIST v1.1.

  OR is defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the 'start date' until the date of the first documentation of progressive disease (PD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

3.2. Secondary Endpoints

3.2.1. Safety endpoints

- AEs as characterized by type, severity (as graded by National Cancer Institute [NCI] CTCAE v.4.03), timing, seriousness, and relationship to study treatments;

  AEs will be graded by the investigator according to the CTCAE v.4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA)

- Laboratory abnormalities as characterized by type, severity (as graded by NCI CTCAE v.4.03) and timing.

3.2.2. Pharmacokinetic endpoints

- PK parameters (C_{max} and C_{trough}).

Table 2. PK Parameters to be Determined for Avelumab, Utomilumab, PF-04518600 and PD 0360324

Parameter	Definition	Method of Determination
C_{max}	Maximum observed plasma concentration	Observed directly from data
C_{trough}	Predose concentration during multiple dosing	Observed directly from data
C_{max}(dn)	Dose normalized C_{max}	C_{max} / Dose

[a] If data permit

3.2.3. Immunogenicity endpoints

- Anti-drug antibody (ADA) levels.

  ADA titers for avelumab and utomilumab (Combination A) or for avelumab and PF-04518600 (Combination B) or for avelumab and PD 0360324 (Combination C) or for avelumab, utomilumab and PF-04518600 (Combination D) or for Avelumab and CMP-001 and utomilumab or PF-04518600 (Combination F).

3.2.4. Efficacy endpoints

- 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);

  TTR is defined, for patients with an OR, as the time from the 'start date' to the first documentation of objective response (CR or PR) which is subsequently confirmed.

  DR is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or death due to any cause.

  PFS is defined as the time from the 'start date' to the date of the first documentation of PD or death due to any cause, whichever occurs first.

  OS is defined as the time from the 'start date' to the date of death due to any cause.

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

  OR is defined as in the primary endpoint section.

3.2.5. Biomarker endpoints

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

Table 3. Biomarker Definition and Determination

Parameter	Definition	Method of Determination
PD-L1 expression	The percent of counted cells scored as PD-L1+ and qualitative assessment of PD-L1 staining on tumor and inflammatory cells as defined by cell morphology in regions of interest	Pathologist, assisted by image analysis
Tumor infiltrating CD8+ lymphocytes	The percent of counted cells that are scored as CD8+	Pathologist, assisted by image analysis

CCI [redacted]

- CCI [redacted]

- CCI [redacted]

3.4. Baseline Variables

3.4.1. Study drug, study treatment and baseline definitions

In this study '**study drug**' refers to avelumab, utomilumab, PF-04518600, PD 0360324 or CMP-001 and '**study treatment**' (or '**treatment group**') refers to one of the following.

Assignment to cohorts A1, A2 or A3, assignment to cohorts A9 or A10, and assignment to cohorts F1, F2 or F3 will be done via randomization. Assignment to all other cohorts is not randomized as described in Section 2.2.

Combination A

- Cohort A1 (Phase 1b/Phase 2 NSCLC): avelumab 10 mg/kg IV Q2W in combination with 500 mg utomilumab IV Q4W
- Cohort A2 (Phase 1b/Phase 2 NSCLC): avelumab 10 mg/kg IV Q2W in combination with 100 mg utomilumab IV Q4W
- Cohort A3 (Phase 1b/Phase 2 NSCLC): avelumab 10 mg/kg IV Q2W in combination with 20 mg utomilumab IV Q4W
- Cohort A4 (Phase 2 Melanoma): avelumab 10 mg/kg IV Q2W in combination with 100 mg utomilumab IV Q4W
- Cohort A5 (Phase 2 SCCHN): avelumab 10 mg/kg IV Q2W in combination with 100 mg utomilumab IV Q4W
- Cohort A6 (Phase 2 TNBC): avelumab 10 mg/kg IV Q2W in combination with 100 mg utomilumab IV Q4W
- Cohort A7 (Phase 2 SCLC): avelumab 10 mg/kg IV Q2W in combination with 100 mg utomilumab IV Q4W
- Cohort A8 (Phase 2 1L NSCLC): avelumab 10 mg/kg IV Q2W in combination with 100 mg utomilumab IV Q4W
- Cohort A9 (Phase 2 1L NSCLC): utomilumab 100 mg IV Q4W followed by utomilumab 100 mg IV Q4W in combination with avelumab 10 mg/kg IV Q2W
- Cohort A10 (Phase 2 1L NSCLC): avelumab 10 mg/kg IV Q2W followed by utomilumab 100 mg IV Q4W in combination with avelumab 10 mg/kg IV Q2W

For Cohorts A4 through A10, the projected utomilumab dose to be used is 100 mg which may be modified based upon emerging safety data for utomilumab from randomized dose cohorts of Combination A.

Combination B

- Cohort B11 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 0.1 mg/kg PF-04518600 IV Q2W
- Cohort B12 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 0.3 mg/kg PF-04518600 IV Q2W
- Cohort B13 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 1 mg/kg PF-04518600 IV Q2W
- Cohort B14 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 3 mg/kg PF-04518600 IV Q2W
- Cohort B21 (Phase 2 NSCLC): avelumab 10 mg/kg IV Q2W in combination with PF-04518600 dose selected at the end of Phase 1b
- Cohort B22 (Phase 2 Melanoma): avelumab 10 mg/kg IV Q2W in combination with PF-04518600 dose selected at the end of Phase 1b (no patients will be enrolled)
- Cohort B23 (Phase 2 SCCHN): avelumab 10 mg/kg IV Q2W in combination with PF-04518600 dose selected at the end of Phase 1b

Combination C

- Cohort C11 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 50 mg PD 0360324 IV Q2W
- Cohort C12 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 100 mg PD 0360324 IV Q2W
- Cohort C13 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 150 mg PD 0360324 IV Q2W
- Cohort C21 (Phase 2 tumor type to be decided among ovarian cancer, SCCHN, NSCLC, gastric cancer): avelumab 10 mg/kg IV Q2W in combination with PD 0360324 dose selected based on Phase 1b (no patients will be enrolled)
- Cohort C22 (Phase 2 tumor type to be decided among ovarian cancer, SCCHN, NSCLC, gastric cancer): avelumab 10 mg/kg IV Q2W in combination with PD 0360324 dose selected based on Phase 1b (no patients will be enrolled)

Combination D

- Cohort D11 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 20 mg utomilumab IV Q4W and 0.1 mg/kg PF-04518600 IV Q2W
- Cohort D12 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 50 mg utomilumab IV Q4W and 0.1 mg/kg PF-04518600 IV Q2W

- Cohort D21 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 20 mg utomilumab IV Q4W and 0.3 mg/kg PF-04518600 IV Q2W
- Cohort D22 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 50 mg utomilumab IV Q4W and 0.3 mg/kg PF-04518600 IV Q2W
- Cohort D31 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 20 mg utomilumab IV Q4W and 1 mg/kg PF-04518600 IV Q2W
- Cohort D32 (Phase1b): avelumab 10 mg/kg IV Q2W in combination with 50 mg utomilumab IV Q4W and 1 mg/kg PF-04518600 IV Q2W
- Cohort D-1 (Phase 2 tumor type to be decided among NSCLC, melanoma, SCCHN, or bladder cancer): avelumab 10 mg/kg IV Q2W in combination with utomilumab and PF-04518600 doses selected based on Phase 1b
- Cohort D-2 (Phase 2 tumor type to be decided among NSCLC, melanoma, SCCHN, or bladder cancer): avelumab 10 mg/kg IV Q2W in combination with utomilumab and PF-04518600 doses selected based on Phase 1b

Combination F

- Cohort F1 (Phase 1b/Phase 2 SCCHN): avelumab 10 mg/kg IV Q2W in combination with 10 mg CMP-001
- Cohort F2 (phase 1b/ Phase 2 SCCHN): avelumab 10 mg/kg IV Q2W in combination with 10 mg CMP-001 and 100 mg utomilumab IV Q4W
- Cohort F3 (Phase 1b/ Phase 2 SCCHN): avelumab 10 mg/kg IV Q2W in combination with 10 mg CMP-001 and 0.3 mg/kg PF-04518600 IV Q2W

CMP-001 will be administered initially as 2 weekly subcutaneous (SC) doses followed by intra tumoral (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).

Start and end dates of study treatment:

The date/time of first dose of study treatment in a combination group is the earliest date/time of the first non-zero dose date/time for the study drugs in the combination.

The date/time of last dose of study treatment in a combination group is the latest date/time of the last non-zero dose date/time for the study drugs in the combination.

Definition of baseline:

Definition of baseline for efficacy analyses in randomized cohorts

The last measurement prior to the ‘start date’ will serve as the baseline measurement for efficacy analyses. If such a value is missing, the last measurement prior to the first dose of study treatment will be used as the baseline measurement except for analyses of tumor assessments data where the baseline assessment would be considered as missing.

Definition of baseline for immunogenicity analyses

The last available assessment prior to the start of treatment with avelumab is defined as 'baseline' result or 'baseline' assessment. If an assessment is planned to be performed prior to the first dose of avelumab in the protocol and the assessment is performed on the same day as the first dose of avelumab, it will be assumed that it was performed prior to avelumab administration, if assessment time point is not collected or is missing.

Definition of baseline for efficacy analyses in non-randomized cohorts and for safety analyses

The last available assessment prior to the start of study treatment is defined as 'baseline' value or 'baseline' assessment for safety and efficacy (for non-randomized cohorts) analyses. If an assessment is planned to be performed prior to the first dose of study treatment in the protocol and the assessment is performed on the same day as the first dose of study treatment, it will be assumed that it was performed prior to study treatment administration, if assessment time point is not collected or is missing. If assessment time points are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. However, if time is missing, an unscheduled assessment on study day 1 will be considered to have been obtained after study treatment administration.

Patients who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1 (one during study and one in the End of Treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Baseline for RR and QT/QTc interval assessments will be derived from the visit where both RR and QT are not missing. Triplicate ECGs are collected in the study and the baseline for each ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. QTcB and QTcF will be derived based on RR and QT. The average of the replicate measurements will be determined after the derivation of the individual parameter at each time point.

3.4.2. Baseline characteristics

Baseline characteristics (including demographics, disease history and prior anti-cancer therapies) are described in Section 6.5.1. These baseline characteristics are not planned to be included as stratification variables or covariates in statistical models unless otherwise specified in Section 6.

3.5. Safety Endpoints

3.5.1. Adverse events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day). The start day of new anti-cancer drug therapy after the first dose of study treatment is derived as outlined in Section 5.2.5.

Adverse Events of Special Interest (AESIs)

AESIs are immune-related adverse events (irAE) and infusion-related reactions (IRRs). For Combination F, AESIs also include Cytokine Release Syndrome. The criteria for classification of an AE as an irAE or IRR are described in Appendix 1 and Appendix 2, respectively.

4. ANALYSIS SETS

Data for all patients will be assessed to determine if patients meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Pfizer's standard operating procedures.

Only patients who signed informed consent will be included in the analysis sets below.

4.1. Full Analysis Set

For the randomized cohorts: The full analysis set (FAS) will include all randomized patients. Patients will be classified according to the study treatment assigned at randomization.

For non-randomized cohorts: The FAS will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one treatment the patient will be classified according to the first study treatment received.

4.2. Safety Analysis Set

For the randomized cohorts: The safety analysis set will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment assigned at randomization unless the incorrect treatment(s) was/were received throughout the dosing period in which case patients will be classified according to the first study treatment received.

For non-randomized cohorts: The safety analysis set will include all patients who receive at least one dose of study drug. Patients will be classified according to the study treatment actually received. If a patient receives more than one study treatment, the patient will be

classified according to the first study treatment received. For the non-randomized cohorts, the FAS and the safety analysis set are identical.

4.3. Other Analysis Set

4.3.1. DLT-evaluable set

This is the primary analysis set for the Phase 1 lead-in 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 study drugs in the combination for reasons other than treatment-related toxicity (eg, missed appointments or development of rapidly progressing disease) are not evaluable for DLT.

4.3.2. PK analysis set

The PK concentration analysis set is a subset of the safety analysis set and will include patients who have at least one post-dose concentration measurement above the lower limit of quantitation (LLQ) for at least one of the study drugs in the combination.

The PK parameter analysis set is a subset of the safety analysis set and will include patients who have at least one of the PK parameters of interest for at least one of the study drugs in the combination.

4.3.3. Biomarker analysis sets

The baseline biomarker analysis set is a subset of the safety analysis set and will include patients who have at least one screening biomarker assessment.

The paired biomarker analysis set is a subset of the safety analysis set and will include patients who have at least one pre-treatment biomarker assessment and one on-treatment assessment of the same biomarker.

Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

4.3.4. Immunogenicity analysis sets

The immunogenicity analysis sets will be per study drug in a combination. The analyses sets are subsets of the safety analysis set and will include patients who have at least one ADA sample collected for each study drug in the combination.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

5.1.1. Hypotheses and sample size determination

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.

Phase 1b lead-in

There is no formal hypothesis testing in this phase. However, 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 treatment groups. The dose level is considered as safe and a treatment group can be expanded when there are not more than 1 of 6 patients with DLTs within the first 2 cycles of treatment.

Phase 2

Hypotheses will be tested separately for each treatment group based on OR rate (ORR, proportion of patients with OR) using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3) and the data from Phase 2 (Cohorts A4, A5). There is no formal hypothesis testing for Cohorts A6, A7, A8, A9, and A10. These cohorts use an estimation approach.

Cohorts A1, A2, A3 (NSCLC)

The null hypothesis will be tested against the alternative hypothesis at the one-sided significance level $\alpha=0.05$ using an exact binomial test

H_0: ORR$\leq$15% vs H_1: ORR>15%.

Within each treatment group, 28 patients will provide at least 80% power to reject the null hypothesis if the true ORR is $\geq$35%.

Cohort A4 (melanoma)

The null hypothesis will be tested against the alternative hypothesis at the one-sided significance level $\alpha=0.05$ using an exact binomial test

H_0: ORR$\leq$15% vs H_1: ORR>15%.

Twenty-eight (28) patients will provide at least 80% power to reject the null hypothesis if the true ORR is $\geq$35%.

Cohort A5 (SCCHN)

The null hypothesis will be tested against the alternative hypothesis at the one-sided significance level α=0.05 using an exact binomial test

H_0: ORR≤20% vs H_1: ORR>20%.

Thirty-five (35) patients will provide at least 80% power to reject the null hypothesis if the true ORR is ≥40%.

Cohort A6 (TNBC), Cohort A7 (SCLC), Cohorts A8, A9, and A10 (1L NSCLC)

Twenty (20) patients each will be enrolled in Cohorts A6, A7, A9 and A10. Overall sample size for Cohort A8 may be larger (up to 26 patients) and can include PD-L1 negative patients that were enrolled prior to Protocol Amendment 6.

With 20 patients in each of the TNBC, SCLC cohorts, and 20 PD-L1 positive patients in 1L NSCLC cohorts, ORR can be estimated with a maximum standard error of 0.112. Table 4 provides the exact binomial 90% confidence intervals (CIs) for ORR based on different possible observed responses in a cohort.

Table 4. Sample Size and Exact 90% CI for ORR in Combination A

N per cohort	Number of responders	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)
	15	75%	(54.4, 89.6)

CI=confidence interval; ORR=objective response rate.

Combination B

Up to 105 patients (Phase 1b and Phase 2 combined) may be enrolled for Combination B treatment.

Phase 1b lead-in

For Phase 1b of this combination, 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.

Phase 2

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 0.10. Table 5 provides the exact binomial 90% CIs for ORR based on different possible observed responses in a cohort.

Table 5. 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%)

CI=confidence interval; ORR=objective response rate.

Combination C

Up to 80 patients (Phase 1b and Phase 2 combined) may be enrolled for Combination C treatment.

Phase 1b lead-in

For Phase 1b of this combination, 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.

Phase 2

For Phase 2 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 5 provides the exact binomial 90% CIs for ORR based on different observed responses in a cohort.

Combination D

Phase 1b lead-in

For Phase 1b of this combination, 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.

Phase 2

For Phase 2 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% within each tumor-specific cohort. Table 5 provides the exact binomial 90% CIs for ORR based on different possible observed responses in a cohort.

Combination F

Up to 20 patients will be randomized in each of the Cohorts F1, F2 and F3 at the selected dose level.

Phase 1b lead-in

There is no formal hypothesis testing in this phase. 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 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.

Phase 2

With 20 patients in each cohort (Phase 1b and 2 combined), 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 are as presented in Table 6.

Table 6. Sample Size and Exact 90% Confidence Intervals for Objective Response Rate in Combination F (Cohorts F1, F2 and 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.

5.1.2. Decision rules

Combination A

Phase 1b lead-in

Table 7 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 treatment group. Conversely, for a DLT that occurs with a rate of 60%, the probability of expanding is 4%.

Table 7. Probability of Expanding Dose

True underlying DLT rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of expanding dose	0.89	0.66	0.42	0.23	0.11	0.04	0.01	<0.01	<0.01

Phase 2

Cohorts A1, A2, A3 (NSCLC)

Within each treatment group using the combined data from the Phase 1b and Phase 2, at the time of the analysis cut-off:

- if there are ≤7 objective responders of 28 patients treated in a given cohort (6+22 patients), 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 a given cohort, the null hypothesis will be rejected and clinically meaningful activity has been demonstrated.

Cohort A4 (melanoma)

At the time of the analysis cut-off:

- if there are ≤7 objective responders out of 28 patients treated 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 out of 28 patients treated in the cohort, the null hypothesis will be rejected and clinically meaningful activity has been demonstrated.

Cohort A5 (SCCHN)

At the time of the analysis cut-off:

- if there are ≤11 objective responders of 35 patients treated 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.

Cohort A6 (TNBC), Cohort A7(SCLC), Cohorts A8, A9, and A10 (1L NSCLC)

There are no formal decision rules.

Combinations B, C and D

Phase 1b lead-in

Dose escalation to identify a safe dose and RP2D of the other immune modulators to be used in combination with avelumab (all 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 (2013)[3], mTPI design is more efficient and safer than the 3+3 design. 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.

Combination F

Phase 1b lead-in

Table 8 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 8. 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.

Phase 2

There are no formal decision rules for the phase 2 of Combinations B, C, D or F.

5.2. General Methods

In this study '**treatment group**' refers to one of the cohorts described in Section 3.4.1. Unless otherwise noted the analyses and summaries will be performed as outlined below

Combinations A and F: combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2 and F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D: Phase1b and from Phase 2 separately and for each combination.

Baseline characteristics, disposition and efficacy data will be summarized based on the FAS by treatment group as noted above.

DLTs will be summarized based on the DLT-evaluable set by treatment group from Phase 1b only. Other safety data, exposure data, concomitant medications and non-drug treatments will be summarized based on the safety analysis set by treatment group as noted above.

PK data will be summarized based on the PK analysis set by treatment group as noted above.

Biomarker data will be summarized based on the biomarker analysis sets by treatment group as noted above.

Immunogenicity data will be summarized based on the immunogenicity analysis set by treatment group as noted above.

5.2.1. Data handling after the cut-off date

Data after the cut-off date may not undergo the cleaning process and will not be displayed in any listings or used for summary statistics, statistical analyses or imputations.

5.2.2. Pooling of centers

In order to provide overall estimates of treatment effects, data will be pooled across centers. The 'center' factor will not be considered in statistical models or for subgroup analyses due to the high number of participating centers in contrast to the anticipated small number of patients randomized/treated at each center.

5.2.3. Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics ie, number of non-missing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile (Q1 and Q3).

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified.

5.2.4. Definition of study day

Start day of study treatment is the day of the first dose of study treatment.

The study day for assessments occurring on or after the start of study treatment (eg, adverse event onset, tumor measurement) will be calculated as:

Study day = Date of the assessment/event - start of study treatment + 1.

The study day for assessments occurring prior to the first dose of study treatment (eg, baseline characteristics, medical history) will be negative and calculated as:

Study day = Date of the assessment/event - start of study treatment.

The study day will be displayed in all relevant data listings.

5.2.5. Definition of start of new anti-cancer drug therapy

Start date of new anti-cancer drug therapy is used to determine the end of the on-treatment period (see Section 5.2.7).

The start date of new anti-cancer drug therapy is the earliest start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages that is after the first dose of study treatment. When start date of anti-cancer drug therapy is missing or partially missing,

the imputation rules described in Section 5.3.3.4 should be applied using only data from the 'Follow-up Cancer Therapy' eCRF pages.

5.2.6. Definition of start of new anti-cancer therapy

Start date of new anti-cancer therapy (drug, radiation, surgery) is used for censoring in efficacy analyses (see Section 6.1.2 and Section 6.2.2).

The start date of new anti-cancer therapy is the earliest date after the 'start date' amongst the following:

- Start date of anti-cancer drug therapy recorded in the 'Follow-up Cancer Therapy' eCRF pages
- Start date of radiation therapy recorded in 'Concomitant Radiation Therapy', and 'Follow-up Radiation Therapy' eCRF pages with 'Treatment Intent' = 'Curative in intent'
- Surgery date recorded in 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages when 'Surgery Outcome' = 'Resected' or 'Partially Resected'.

When start date of anti-cancer therapy is missing or partially missing, the imputation rules described in Section 5.3.3.4 should be applied using 'Follow-up Cancer Therapy', 'Concomitant Radiation Therapy', 'Follow-up Radiation Therapy', 'Concomitant Surgery', and 'Follow-up Surgery' eCRF pages.

5.2.7. Definition of on-treatment period

Safety endpoints will be summarized based on the on-treatment period unless otherwise specified.

On-treatment period is defined as the time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day).

Safety data collected outside the on-treatment period as described above will be listed and flagged in listings but not summarized.

5.2.8. Standard derivations and reporting conventions

The following conversion factors will be used to convert days into weeks, months or years: 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

Demographics and physical measurements:

- Age [years]:
  - (date of given informed consent - date of birth + 1) / 365.25
  - In case of missing day, day only: Age [years]: (year/month of given informed consent – year/month of birth)

- In case only year of birth is given: Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

- BMI (kg/m^2) = weight (kg)/[height (m)]^2
- BSA (m^2) = ([height (cm) × weight (kg)] / 3600)$^{0.5}$

For reporting conventions, mean and median should generally be displayed one more decimal place than the raw data and standard deviation should be displayed to two more decimal places than the raw data. Percentages will be reported to one decimal place. The rounding will be performed to closest integer / first decimal using the common mid-point between the two consecutive values. Eg, 5.1 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6.

5.2.9. Unscheduled visits

Generally, data collected at unscheduled visits will be included and analyzed for both safety and efficacy analyses in the same fashion as the data collected at scheduled visits except where otherwise noted in the sections that follow. Descriptive statistics (mean, SD, median, minimum, maximum, quartiles) by nominal visit or time point for safety endpoints such as laboratory measurements, ECGs and vital signs will include only data from scheduled visits.

5.2.10. Adequate baseline tumor assessment

Adequate baseline is defined using the following criteria:

- All baseline assessments must be within 28 days prior to and including ‘start date’.
- All documented lesions must have non-missing assessments (ie, non-missing measurements for target lesions and non-missing lesions assessment status at baseline for non-target lesions).

5.2.11. Adequate post-baseline tumor assessment

An adequate post-baseline assessment is defined as an assessment where a response of CR, PR, SD, non-CR/non-PD, or PD can be determined (see Section 6.1.2.1). Time points where the response is not evaluable (NE) or no assessment was performed will not be used for determining the censoring date.

5.3. Methods to Manage Missing Data

5.3.1. Missing data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used.

In all patient data listings imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, eg when they cannot be calculated, should be presented as 'ND' or 'NA'. For example, if N=1, the measure of variability (SD) cannot be computed and should be presented as 'ND' or 'NA'.

5.3.1.1. Pharmacokinetic concentrations

Concentrations Below the Limit of Quantification

For all calculations, figures and estimation of individual pharmacokinetic parameters, all concentrations assayed as below the level of quantification (BLQ) will be set to zero. In log-linear plots these values will not be represented. The BLQ values will be excluded from calculations of geometric means and their CIs. A statement similar to 'All values reported as BLQ have been replaced with zero' should be included as a footnote to the appropriate tables and figures.

Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, concentrations will be set to missing if one of the following cases is true:

1. A concentration has been reported as ND (ie, not done) or NS (ie, no sample);
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged as anomalous by the clinical pharmacologist.

Summary statistics will not be presented at a particular time point if more than 50% of the data are missing. For analysis of pharmacokinetic concentrations, no values will be imputed for missing data.

5.3.1.2. Pharmacokinetic parameters

Whether actual or nominal PK sampling time will be used for the derivation of PK parameters will be determined by the results of interim PK analyses. If a PK parameter cannot be derived from a patient's concentration data, the parameter will be coded as NC (ie, not calculated). NC values will not be generated beyond the day that a patient discontinues.

In summary tables, statistics will be calculated by setting NC values to missing. Statistics will not be presented for a particular treatment if more than 50% of the data are NC. For statistical analyses (ie, analysis of variance), PK parameters coded as NC will also be set to missing.

If an individual patient has a known biased estimate of a PK parameter (due for example to a deviation from the assigned dose level), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

5.3.2. Handling of incomplete dates

5.3.2.1. Disease history

Incomplete dates for disease history (eg, initial diagnosis date, date of documented, locally advanced, inoperable or metastatic disease diagnosis, date of response or progression in prior treatment) will be imputed as follows:

- If the day is missing, it will be imputed to the 15th day of the month.
- If both day and month are missing and the year is prior to the year of the first study treatment, the month and day will be imputed as July 1st.
- If both day and month are missing and the year is same as the year of the first study treatment, the month and day will be imputed as January 1st.
- If the date is completely missing, no imputation will be performed.

5.3.2.2. Adverse events

Incomplete AE-related dates will be imputed as follows:

- If the AE onset date is missing completely, then the onset date will be replaced by the start of study treatment.
- If only the day part of the AE onset date is missing, but the month and year are equal to the start of study treatment, then the AE onset date will be replaced by the start of study treatment. For example, if the AE onset date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed AE onset date will be 15/JAN/2015.
- If both the day and month of the AE onset date are missing but the onset year is equal to the start of study treatment, then the onset date will be replaced by the start of study treatment. For example, if AE onset date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed AE onset date will be 19/NOV/2014.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete stop date will not be imputed. If stop date of AE is after the date of cut-off outcome of AE is ongoing at cut-off.

5.3.2.3. Prior and concomitant medications

Incomplete prior/concomitant medication dates will be imputed as follows:

- If the medication date is missing completely, then the medication date will be replaced by the start of study treatment.
- If the day of medication date is missing, but the month and year are equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/JAN/2015, and study treatment start date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015.

- If both the day and month of medication start date are missing but the start year is equal to the start of study treatment, then the medication date will be replaced by the start of study treatment. For example, if the medication start date is --/---/2014, and study treatment start date is 19/NOV/2014, then the imputed medication start date will be 19/NOV/2014.
- In all other cases the missing medication day or missing medication month will be replaced by 1.
- Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete stop date.
- In all other cases the incomplete medication stop date will not be imputed.

5.3.2.4. Exposure

No imputation will be done for first dose date. Date of last dose of study drug, if unknown or partially unknown, will be imputed as follows:

- If the last date of study drug is completely missing and there is no End of Treatment eCRF page and no death date, the patient should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date
- If the last date of study drug is completely or partially missing and there is EITHER an End of Treatment eCRF page OR a death date available (within the cut-off date), then imputed last dose date is:

  = 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

  = Last day of the month, if both Year and Month are available and Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

  = min (EOT date, death date), for all other cases.

5.3.3. Imputation rules for date of last contact and efficacy assessments

5.3.3.1. Date of last contact

The date of last contact will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (blood draws (laboratory, PK), vital signs, performance status, ECG, tumor assessments)
- Start and end dates of anti-cancer therapies administered after study treatment discontinuation
- AE start and end dates
- Last date of contact collected on the ‘Survival Follow-up’ eCRF (do not use date of survival follow-up assessment unless status is ‘alive’)
- Study drug start and end dates
- Randomization date

- Withdrawal of consent date
- Date of discontinuation on disposition eCRF pages (do not use if reason for discontinuation is lost to follow-up).

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cut-off date will not be applied to derive the last contact date.

5.3.3.2. Death date

Missing or partial death dates will be imputed based on the last contact date:

- If the date is missing it will be imputed as the day after the date of last contact
- If the day or both day and month is missing, death will be imputed to the maximum of the full (non-imputed) day after the date of last contact and the following:
  - Missing day: 1st day of the month and year of death
  - Missing day and month: January 1st of the year of death

5.3.3.3. Tumor assessments

All investigation dates (eg, X-ray, CT scan) must be completed with day, month and year.

If there are multiple scan dates associated with an evaluation, ie, radiological assessments occur over a series of days rather than the same day, the choice of date of assessment could impact the date of progression and/or date of response. If there are multiple scan dates associated with an evaluation, the earliest of the scan dates associated with the evaluation will be used as the date of assessment.

If one or more investigation dates for an evaluation are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the earliest of all investigation dates (eg, X-ray, CT-scan).

If all measurement dates for an evaluation have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations for an evaluation, the respective assessment will be considered to be at the date which is exactly between the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations.

5.3.3.4. Date of start of new anti-cancer therapy

Incomplete dates for start date of new anti-cancer therapy (drug therapy, radiation, surgery) will be imputed as follows and will be used for determining censoring dates for efficacy analyses and in the derivation of the end of on-treatment period. PD date below refers to PD date by investigator assessment.

- The end date of new anti-cancer therapy will be included in the imputations for start date of new anti-cancer therapy. If the end date of new anti-cancer therapy is
  - completely missing then it will be ignored in the imputations below
  - partially missing with only year (YYYY) available then the imputations below will consider 31DECYYYY as the end date of the new anti-cancer therapy
  - partially missing with only month and year available then the imputations below will consider the last day of the month for MMMYYYY as the end date of the new anti-cancer therapy
- For patients who have not discontinued study treatment at the analysis cut-off date, last dose of study treatment is set to the analysis cut-off date in the imputations below.
- If the start date of new anti-cancer therapy is completely or partially missing, then the imputed start date of new anti-cancer therapy is derived as follows:
  - Start date of new anti-cancer therapy is completely missing

    Imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]
  - Only year (YYYY) for start of anti-cancer therapy is available

    IF YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy] THEN imputed start date = 31DECYYYY;

    ELSE IF YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    ELSE IF YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

    THEN imputed start date = 01JANYYYY
  - Both Year (YYYY) and Month (MMM) for start of anti-cancer therapy are available

    IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

    MMM < Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

    THEN

    imputed start date = DAY (Last day of MMM) MMM YYYY;

    ELSE IF

    YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM = Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]);

ELSE IF

YYYY = Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy], AND

MMM > Month of min [max(PD date + 1 day, last dose of study treatment + 1 day), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY;

ELSE IF

YYYY < Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = DAY (Last day of MMM) MMM YYYY;

ELSE IF

YYYY > Year of min [max(PD date + 1, last dose of study treatment + 1), end date of new anti-cancer therapy]

THEN

imputed start date = 01 MMM YYYY.

6. ANALYSES AND SUMMARIES

Refer to Section 4 for definitions of analysis sets and Section 5.2 for general methodology.

6.1. Primary Endpoints

6.1.1. DLT for Phase 1b lead-in

6.1.1.1. Primary analysis

The following analyses will be based on the DLT-evaluable set for patients in the Phase 1b for all combinations. DLTs will be listed and summarized by treatment group for Phase 1b cohorts.

6.1.2. Confirmed OR as assessed by the Investigator per RECIST v1.1 for Phase 2

6.1.2.1. Primary analysis

Combinations A and F

The following analyses will be based on the FAS by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following analyses will be based on the FAS by treatment group using the data from Phase 2 Cohorts for each combination.

Assessment of response will be made as per investigator using RECIST v1.1.

Best overall response (BOR) will be assessed based on reported overall lesion responses at different evaluation time points from the 'start date' until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies will be considered in the assessment of BOR. Clinical deterioration will not be considered as documentation of disease progression.

BOR Based on Confirmed Responses:

- CR = at least two determinations of CR at least 4 weeks apart and before first documentation of PD
- PR = at least two determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before first documentation of PD (and not qualifying for a CR)
- SD (applicable only to patients with measurable disease at baseline) = at least one SD assessment (or better) ≥ 6 weeks after the 'start date' and before first documentation of PD (and not qualifying for CR or PR)
- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline) = at least one non-CR/non-PD assessment (or better) ≥ 6 weeks after the 'start date' and before first documentation of PD (and not qualifying for CR or PR).
- PD = first documentation of PD ≤ 12 weeks after the 'start date' (and not qualifying for CR, PR, SD or non-CR/non-PD)
- NE: all other cases.

An objective status of PR or SD cannot follow one of CR. SD can follow PR only in the rare case that tumor increases by less than 20% from the nadir, but enough that a previously documented 30% decrease from baseline no longer holds. If this occurs, the sequence PR-SD-PR is considered a confirmed PR. A sequence of PR – SD – SD – PD would be a best response of SD if the window for SD definition has been met.

Objective Response (OR) is defined as confirmed BOR of CR or PR according to RECIST v1.1.

Patients who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-cancer therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each patient will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of patients with OR in the analysis set.

A formal test of hypothesis for each treatment group (Cohorts A1, A2, A3, A4, and A5 only) in Combination A will be performed at the 1-sided significance level α=0.05 based on the exact binomial test as described in Section 5.1.1.

ORR by treatment group will also be calculated along with the 2-sided 90% CI using the Clopper-Pearson method [2] (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option). Two-sided 95% CIs will also be calculated and reported.

In addition, the frequency (number and percentage) of patients with a confirmed BOR of CR, PR, SD, non-CR/non-PD (applicable only to patients with non-measurable disease at baseline), PD, and NE will be tabulated. Patients with confirmed BOR of NE will be summarized by reason for having NE status. The following reasons will be used:

- No baseline assessment
- No post-baseline assessments due to death
- No post-baseline assessments due to other reasons
- All post-baseline assessments have overall response NE
- New anti-cancer therapy started before first post-baseline assessment
- SD of insufficient duration (<6 weeks after the 'start date' without further evaluable tumor assessments)
- PD too late (>12 weeks after the 'start date')

Special and rare cases where BOR is NE due to both SD of insufficient duration and late PD will be classified as 'SD of early' (ie, SD of insufficient duration).

6.2. Secondary Endpoint(s)

6.2.1. Safety endpoints

Refer to Section 6.6.

6.2.2. Efficacy endpoints

Combinations A and F

The following analyses will be based on the FAS by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2 and F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following analyses will be based on the FAS by treatment group using the data from Phase1b and from Phase 2 separately and for each combination.

Tumor-related endpoints will be analyzed based on investigator assessment using RECIST v1.1. In addition to what is described below, the objective response (OR) will also be analyzed similar to that described in Section 6.1.2.1 for each of the Phase 1b cohorts of Combinations B, C and D.

6.2.2.1. Tumor shrinkage from baseline

Tumor shrinkage will be summarized as the percent change from baseline in target lesions (sum of longest diameter for non-nodal lesion and short axis for nodal lesion) per time point. It will be derived as:

- ((Sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

The maximum reduction in target lesions from baseline will be derived across all the post-baseline assessments until documented disease progression, excluding assessments after start of subsequent anti-cancer therapy, as:

- Minimum of ((sum of target lesions at week XX – sum of target lesions at baseline)/sum of target lesions at baseline) × 100

A waterfall plot of maximum percent reduction in the sum of longest diameter for non-nodal lesions and short axis for nodal lesions from baseline will be created by treatment group. These plots will display the best percentage change from baseline in the sum of the diameters of all target lesions for each patient with measurable disease at baseline and at least one post-baseline assessment.

6.2.2.2. Disease control

Disease Control (DC) is defined as BOR of CR, PR, non-CR/non-PD or SD. DC rate (DCR) is the proportion of patients with DC.

DCR will be summarized by frequency counts and percentages.

6.2.2.3. Duration of response

Duration of Response (DR) is defined, for patients with OR, as the time from the first documentation of objective response (CR or PR) to the date of first documentation of PD or

death due to any cause. If a patient has not had an event (PD or death), DR is censored at the date of last adequate tumor assessment. The censoring rules for DR are described in Table 9.

DR (months) = [date of event or censoring– first date of OR +1]/30.4375

Table 9. Outcome and Event Dates for DR Analyses

Scenario	Date of event/censoring	Outcome
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the 'start date'	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New nti-cancer therapy given	Date of last adequate tumor assessment [a] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the 'start date'; if the criteria were met the censoring will be on the 'start date'.

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median DR time with 2-sided 95% CIs. In particular, the DR rates at 2, 4, 6, 8, 10 and 12 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[4] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

DR will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with OR is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 10 following the hierarchy shown.

Table 10. DR Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	Start of new anti-cancer therapy	Start of new anti-cancer therapy
2	Event after 2 or more missing or inadequate post-baseline tumor assessments/date of randomization	Event after 2 or more missing assessments [a]
3	No event and [withdrawal of consent date ≥ date of randomization OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
4	No event and lost to follow-up in any disposition page	Lost to follow-up
5	No event and [EOS present OR disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
6	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

6.2.2.4. Time to response

Time to response (TTR) is defined, for patients with OR, as the time from the 'start date' to the first documentation of objective response (CR or PR) which is subsequently confirmed.

TTR (in months) = [first date of OR – 'start date' +1]/30.4375

TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

6.2.2.5. Progression-free survival

Progression-Free Survival (PFS) is defined as the time from the 'start date' to the date of the first documentation of PD 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 a new anti-cancer therapy prior to an event (see Section 5.2.6) or for patients with an event after 2 or more missing tumor assessments. Patients who do not have an adequate baseline tumor assessment or who do not have an adequate post-baseline tumor assessment will be censored on the 'start date' unless death occurred on or before the time of the second planned tumor assessment (ie ≤ 16 weeks after the 'start date') in which case the death will be considered an event.

In this study antitumor activity will be assessed through radiological tumor assessments conducted at screening and every 8 weeks (±7 days) until PD regardless of initiation of subsequent anti-cancer therapy. After 1 year from the 'start date', tumor assessments will be

conducted at 12-week (±7 days) intervals and after 2 years from the 'start date', tumor assessments will be conducted at 16-week (±7 days) intervals.

The censoring and event date options to be considered for the PFS and DR analysis are presented in Table 11.

PFS (months) = [date of event or censoring– 'start date' +1]/30.4375

Table 11. Outcome and Event Dates for PFS Analyses

Scenario	Date of event/censoring	Outcome
No adequate baseline assessment	'Start date' [a]	Censored [a]
PD or death - After at most one missing or inadequate post-baseline tumor assessment, OR - ≤ 16 weeks after the 'start date'	Date of PD or death	Event
PD or death - After 2 or more missing or inadequate post-baseline tumor assessments	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
No PD and no death	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored
Treatment discontinuation due to 'Disease progression' without documented progression	Not applicable	Information is ignored. Outcome is derived based on documented progression only.
New anti-cancer therapy given	Date of last adequate tumor assessment [b] documenting no PD before new anti-cancer therapy is given or missed tumor assessments	Censored

[a] However if the patient dies ≤16 weeks after the 'start date' the death is an event with date on death date

[b] If there are no adequate post-baseline assessments prior to PD or death, then the time without adequate assessment should be measured from the 'start date'; if the criteria were met the censoring will be on the 'start date'

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median PFS time with 2-sided 95% CIs. In particular, the PFS rate at 2, 4, 6, 8, 10, 12 and 18 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[4] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with each event type (PD or death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 12 following the hierarchy shown.

Table 12. PFS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No adequate baseline assessment	No adequate baseline assessment
2	Start of new anti-cancer therapy	Start of new anti-cancer therapy
3	Event after 2 or more missing or inadequate post-baseline tumor assessments/'start date'	Event after missing assessments [a]
4	No event and [withdrawal of consent date ≥ 'start date' OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
5	No event and lost to follow-up in any disposition page	Lost to follow-up
6	No event and [EOS present OR disposition page for any epoch after screening says patient will not continue into any subsequent phase of the study] and no adequate post-baseline tumor assessment	No adequate post-baseline tumor assessment
7	No event and none of the conditions in the prior hierarchy are met	Ongoing without an event

[a] 2 or more missing or inadequate post-baseline tumor assessments.

The PFS time or censoring time and the reasons for censoring will also be presented in a patient listing.

6.2.2.6. Overall Survival

Overall survival (OS) is defined as the time from the 'start date' to the date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

OS (months) = [date of death or censoring– 'start date' +1]/30.4375

Kaplan-Meier estimates (product-limit estimates) will be presented by treatment group together with a summary of associated statistics including the median OS time with 2-sided 95% CIs. In particular, the OS rate at 2, 4, 6, 8, 10, 12, 18 and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[4] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Frequency (number and percentage) of patients with an event (death) and censoring reasons will be presented by treatment group. Reasons for censoring will be summarized according to the categories in Table 13 following the hierarchy shown.

Table 13. OS Censoring Reasons and Hierarchy

Hierarchy	Condition	Censoring Reason
1	No event and [withdrawal of consent date ≥ 'start date' OR End of study (EOS) = Patient refused further follow-up]	Withdrawal of consent
2	No event and [lost to follow-up in any disposition page OR data cut-off date – last contact date > 16 weeks]	Lost to follow-up
3	No event and none of the conditions in the prior hierarchy are met	Alive

The OS time or censoring time and the reasons for censoring will also be presented in a patient listing.

OS analysis will be conducted for patients up to LSLV of the study.

6.2.3. Pharmacokinetic endpoints

Combinations A and F

The following pharmacokinetic analyses will be based on the PK analyses set by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following pharmacokinetic analyses will be based on the PK analyses set by treatment group using the data from Phase 1b and from Phase 2 separately and for each combination.

C_{trough} and C_{max} for avelumab for all combinations, utomilumab (for Combination A and D), PF-04518600 (for Combinations B and D), and PD 0360324 (for Combination C) will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by treatment group, 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

Pharmacokinetic parameters for avelumab, utomilumab, PF-04518600 and PD 0360324 will be taken from observed values or derived from plasma concentration-time data as described in Section 3.2.2.

Presentation of pharmacokinetic data will include:

- Descriptive statistics (n, mean, SD, %CV, median, minimum, maximum) of plasma concentrations will be presented in tabular form by treatment group, dose level, cycle, day and nominal time. Additionally, similar descriptive statistics will also be generated

for dose-normalized utomilumab (Combination A and D), PF-04518600 (Combination B and D), PD 0360324 (Combination C) pharmacokinetic parameters, if appropriate.

- Pharmacokinetic parameters for avelumab, utomilumab, PF-04518600, and PD 0360324 will be listed and summarized by treatment group/dose level, cycle and study day using descriptive statistics (n, mean, SD, %CV, median, minimum, maximum, geometric mean and its associated %CV, and 95% CI). For T_{max}, the range (min, max) will also be provided. PK parameters with zero values will be excluded from the calculation of geometric means and its associated %CV. If an intrapatient dose escalation or reduction occurs, dose-dependent PK parameters (C_{max}) for that patient may be dose-normalized when it is known that the drug exhibits linear PK within the dose range and other PK parameters will be reported as estimated; or may only be included in descriptive statistics and summary plots up to the time of the dose change. In addition, dose-normalized C_{max} and C_{trough} parameters will be summarized (as described above) using data pooled across treatment groups in which different utomilumab doses, PF-04518600 doses or PD 0360324 doses were administered, if appropriate.

6.2.4. Population pharmacokinetic endpoints

Pharmacokinetic and pharmacodynamic 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 and utomilumab (Combination A), avelumab and PF-04518600 (Combination B), avelumab and PD 0360324 (Combination C) or avelumab, utomilumab and PF-04518600 (Combination D) or Avelumab (Combination F) exposure and biomarkers or significant safety/efficacy endpoints. The results of these analyses, if performed, may be reported separately.

6.2.5. Biomarker Endpoints

Combinations A and F

The following biomarker analyses will be based on the biomarker analysis sets by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following biomarker analyses will be based on the biomarker analysis sets by treatment group using the data from Phase 1b and from Phase 2 separately and for each combination.

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.

6.2.6. Endpoints for immunogenicity data of avelumab and other study drugs

Combinations A and F

The following analyses of immunogenicity data will be based on the Immunogenicity analysis set by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following analyses of immunogenicity data will be based on the Immunogenicity analysis set by treatment group using the data from Phase 1b and from Phase 2 separately and for each combination.

Blood samples for avelumab and other study drug immunogenicity testing will be collected as outlined in the "Schedule for Pharmacokinetic Sample Collection" table of the Schedule of Assessments section of the protocol.

Patients will be characterized into different ADA categories based on the criteria defined in Table 14.

Table 14. Patients Characterized Based on Anti-Drug Antibody Results (ADA Status)

Category	Definition	Patients at Risk (Denominator for Incidence)
ADA never-positive	No positive ADA results at any time point; ADA-negative patients (titer < cutpoint)	Number of patients with at least one valid ADA result at any time point
ADA ever-positive	At least one positive ADA result at any time point; ADA-positive patients (titer ≥ cutpoint)	Number of patients with at least one valid ADA result at any time point
Baseline ADA positive	A positive ADA result at baseline	Number of patients with valid baseline ADA result
Treatment-boosted ADA	A positive ADA result at baseline and the titer ≥ 8×baseline titer at least once after treatment with avelumab	Number of patients with valid baseline ADA results and at least one valid post-baseline ADA result
Treatment-induced ADA	Patient is ADA-negative at baseline and has at least one positive post-baseline ADA result; or if patient does not have a baseline sample, the patient has at least one positive past-baseline ADA result	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Transient ADA response	If patients with treatment-induced ADA have (a single positive ADA result or duration between first and last positive result <16 weeks) and ADA result at the last assessment is not positive.	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)
Persistent ADA response	If patients with treatment-induced ADA have duration between first and last positive ADA result ≥16 weeks or a positive ADA result at the last assessment	Number of patients with at least one valid post-baseline ADA result and without positive baseline ADA result (including missing, NR)

ADA: anti-drug antibody, NR = not reportable.

The number and percentage of patients in each ADA category will be summarized.

6.2.6.1. Time to and Duration of ADA response

The ADA analyses described below will include patients with treatment-induced ADA.

Time (weeks) to ADA response is defined as:

(Date of first positive ADA result – date of first dose of avelumab + 1)/7.

Time to ADA response will be summarized using simple descriptive statistics (mean, SD, median, min, max. Q1, Q3).

Duration (weeks) of ADA response is defined as:

(Date of last positive ADA result – date of first positive ADA result + 1)/7.

Duration of ADA response will be censored if:

- the last ADA assessment is positive AND patient is ongoing treatment with avelumab, or
- the last ADA assessment is positive AND patient discontinued treatment with avelumab.

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median ADA response time with 2-sided 95% CIs. ADA response rates at different timepoints will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982)[1] and the CIs for the survival function estimates will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002)[4] (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Duration of ADA response will be displayed graphically and analyzed using Kaplan-Meier methodology. If the number of patients with ADA response is small, the Kaplan-Meier method may not provide reliable estimates. In this case, only descriptive statistics or listings will be provided

6.2.6.2. ADA titer

For patients who are ADA ever positive, the maximum observed ADA titer for a patient will be summarized, overall and by ADA subcategories (baseline ADA positive, treatment-boosted ADA, treatment-induced ADA, transient ADA response, persistent ADA response) of patients having each discrete maximum titer value will be tabulated. The denominator to calculate the percentages will be the total number of patients in the associated ADA subcategory.

For patients with treatment-induced ADA, a cross tabulation of duration of ADA response and maximum ADA titer will be provided. The following categories for duration of ADA response will be used: ≤1, >1 to ≤3, >3 to ≤5, >5 to ≤7, >7 to ≤13, >13 to ≤16, >16 to ≤25, >25 weeks. In this categorization, the censoring in duration of ADA response is ignored.

6.2.6.3. Analysis of PK by immunogenicity status

The following ADA status will be used for the analyses described below.

ADA

- ADA ever-positive versus ADA never-positive
- ADA: treatment-induced ADA versus ADA never-positive or baseline ADA positive

PK parameters and immunogenicity status

The following analyses will include patients in both the immunogenicity analysis set and in the PK parameter analysis set. The PK endpoints pertinent to the immunogenicity analyses are C_{trough} and C_{max}. Blood samples for avelumab, utomilumab, PF-04518600, and PD 0360324 PK will be collected as outlined in the "Schedule for Pharmacokinetic Sample Collection" table of the Schedule of Assessments section of the protocol.

C_{trough} and C_{max} will be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by nominal time and ADA status. Linear-linear plots of mean and median for C_{trough} and C_{max} over nominal time and by ADA status will be presented.

Among patients with treatment-induced ADA, analyses will be conducted to assess whether C_{trough} and C_{max} have any changes before and after the first positive ADA assessment. To be included in this analysis, patients must have the same PK parameter available both before and after the first positive ADA assessment. Relative PK day will be calculated as:

(PK assessment nominal day) – (first positive ADA assessment nominal day).

Nominal day is the protocol scheduled timing for an assessment. For example, if C_{trough} is collected on Day 1 of Cycle 2 and the first positive ADA result is observed on Day 1 of Cycle 3, then the relative PK day for this C_{trough} is -28. Linear-linear plots of mean and median for C_{trough} and C_{max} over relative PK day will be presented.

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.4. Subset Analyses

ORR and DR (if meaningful) will be summarized in the following subsets within each treatment group:

- general prior anti-cancer immuno-therapy (Yes, No)
- Checkpoint inhibitors
  - prior PD-1/PD-L1 therapy (Yes, No)

- prior anti-CTLA4 therapy (Yes, No)
- prior checkpoint inhibitor status (relapsed/resistant, refractory, naïve)
  - naïve: has not previously received a checkpoint inhibitor
  - resistant/relapse: progressed after SD or better
  - refractory: BOR of PD

- HPV status (positive, negative) for SCCHN patients
- PD-L1 status (positive, negative, unknown) at baseline

For CD8, descriptive statistics will be provided by objective response category.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline summaries

Combinations A and F

The following analyses will be based on the FAS overall and separately by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following analyses will be based on the FAS overall and separately by treatment group using the data from Phase1b and from Phase 2 separately and for each combination.

6.5.1.1. Demographic characteristics

Demographic characteristics will be summarized by treatment group using the following information from the 'Screening/Baseline Visit' eCRF pages.

- Demographic characteristics
  - Gender: Male, Female
  - Race: White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Unknown
  - Ethnic origin:
    - Hispanic or Latino
    - Not Hispanic or Latino
  - Age (years): summary statistics
  - Age categories:
    - < 65 years, ≥ 65 years

  - < 65, 65-<75, 75-<85, ≥ 85 years
- Pooled Geographical Region (as applicable):
  - North America
  - Europe
  - Asia
  - Rest of the World (Australasia, Latin America, Africa and/or Middle East will be included as additional pooled geographical regions if including > 10% of the overall randomized/treated population)
- Geographic Region (as applicable):
  - North America
  - Latin America
  - Western Europe
  - Eastern Europe
  - Middle East
  - Australasia
  - Asia
  - Africa
- Eastern Cooperative Oncology Group (ECOG) Performance Status: 0, 1, 2, 3, and 4

- Baseline disease status
  - HPV status (positive, negative) for SCCHN patients

Center codes will be used for the determination of the patient's geographic region.

The listing of demographics and baseline characteristics will include the following information: patient identifier, treatment group, age, sex, race, ethnicity, and ECOG performance status.

6.5.1.2. Medical history

Medical history will be coded using the most current available version of Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized from the 'Medical History' eCRF page. Medical history will be summarized as the numbers and percentages of patients by MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) as summary category. Each patient will be counted only once within each PT or SOC.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

6.5.1.3. Disease characteristics

Information on disease characteristics collected on 'Primary Diagnosis' and RECIST eCRF pages will be summarized overall and by treatment group. Summary statistics will be presented for the following.

From the 'Primary Diagnosis' eCRF page:

- Site of primary tumor
- Primary diagnosis (summarize all categories collected in the 'Primary Diagnosis' eCRF page)
- Time since initial diagnosis to 'start date' (months), defined as ('start date' – date of initial diagnosis)/30.4375
- Time since diagnosis of local/regional recurrence of disease (months), defined as ('start date' – date of diagnosis of local/regional recurrence of disease)/30.4375

From the RECIST eCRF page:

- Measurable disease (lesions) at baseline (Yes, No)
- Involved tumor sites at baseline

Listing of disease history will be provided with all relevant data (as collected on the 'Primary Diagnosis' eCRF pages) and derived variables as above.

6.5.1.4. Prior anti-Cancer therapies

The prior anti-cancer therapies are collected under the 'Prior Cancer Therapy', 'Prior Radiation Therapy' and 'Prior Surgery' eCRF pages.

The number and percentage of patients in each of the following anti-cancer therapy categories will be tabulated:

- Patients with at least one type of prior anti-cancer treatment
- Patients with at least one prior anti-cancer drug therapy
- Patients with at least one prior anti-cancer radiotherapy
- Patients with at least one prior anti-cancer surgery

Prior anti-cancer drug therapy will be summarized as follows based on the number and percentage of patients with the following:

- At least one prior anti-cancer drug therapy
- Number of prior anti-cancer drug therapy regimens: missing, 1, 2, 3, ≥4 for metastatic disease

- Prior anti-cancer immune therapy (including PD-1, PD-L1, anti-CTLA4, others)
- Intent of Drug Therapy: Neo-Adjuvant, Adjuvant, Advanced / Metastatic, Locoregional disease /Recurrence
- Best response: CR, PR, SD, PD, Unknown, Not applicable. Best response is derived from the last treatment regimen.

The prior anti-cancer drug therapies will also be summarized based on the number and percentage of patients by the drug class and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. The summary will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used.

Prior anti-cancer drug therapies will be included in the listings that follow with a flag to identify prior therapies. These will include the patient identification number, and all the relevant collected data-fields on the corresponding eCRF pages.

- Listing of anti-cancer drug therapies

6.5.2. Study conduct and patient disposition

Combinations A and F

The following analyses will be performed based on the FAS overall and separately by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combination B, C and D

The following analyses will be performed based on the FAS overall and separately by treatment group using the data from Phase 1b and Phase 2 separately and for each combination.

6.5.2.1. Patient disposition

For randomized cohorts

The percentages below will be calculated based on the number of patients in the FAS.

- Total number of patients screened overall
- Number of patients who discontinued from the study prior to randomization overall and by the main reason for discontinuation
- Number and percentage of randomized patients in each of the analysis sets defined in Section 4
- Number and percentage of randomized patients with study drug ongoing (separately for each study drug when administered in combination)

- Number and percentage of randomized patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug when administered in combination)
- Number and percentage of patients who entered follow-up
- Number and percentage of patients who discontinued follow-up overall and by the main reason for discontinuation
- Number and percentage of patients who entered long-term follow-up
- Number and percentage of patients who discontinued long-term follow-up overall and by the main reason for discontinuation

The results of the randomization algorithm will be summarized as follows:

- Number and percentage of randomized patients overall, by region (Europe, EEA (required by EudraCT), North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region
- Number and percentage of randomized patients by center
- Cross tabulation: patients randomized vs. patients treated (Cohorts A1, A2 and A3, Cohorts A9 and A10, and Cohorts F1, F2 and F3)

For non-randomized cohorts

The percentages below will be calculated based on the number of patients in the FAS.

- Total number of patients screened overall
- Number of patients who discontinued from the study prior to treatment with study drug overall and by the main reason for discontinuation
- Number and percentage of treated patients in each of the analysis sets defined in Section 4
- Number and percentage of patients with study drug ongoing (separately for each study drug when administered in combination)
- Number and percentage of patients who discontinued study drug overall and by the main reason for discontinuation of study drug (separately for each study drug when administered in combination)
- Number and percentage of patients who entered follow-up
- Number and percentage of patients who discontinued follow-up overall and by the main reason for discontinuation
- Number and percentage of patients who entered long-term follow-up

- Number and percentage of patients who discontinued long-term follow-up overall and by the main reason for discontinuation

In addition, the following will be summarized:

- Number and percentage of treated patients overall, by region (Europe, EEA (required by EudraCT), North America, Latin America, Middle East, Asia, Australasia, Africa), by country within region
- Number and percentage of treated patients by center

6.5.2.2. Protocol deviations

All protocol violations that impact the safety of the patients and/or the conduct of a study and/or its evaluation will be reported. These include:

- Patients who are dosed on the study despite not satisfying the inclusion criteria
- Patients who develop withdrawal criteria whilst on the study but are not withdrawn
- Patients who receive the wrong treatment or an incorrect dose
- Patients who receive an excluded concomitant medication
- Deviations from GCP

The identification of these and other CSR-reportable deviations will be based on the inclusion/exclusion criteria or other criteria presented in the protocol.

6.5.3. Study treatment compliance and exposure

Combinations A and F

The following analyses will be based on the safety analysis set by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following analyses will be based on the safety analysis set by treatment group using the data from Phase1b and from Phase 2 separately and for each combination.

Cycle definitions for study drugs that are administered in combination apply to all the study drugs in the combination. Ie, cycle is patient-dependent, rather than study-drug-dependent when study drugs are administered in combination.

For Cycle X, actual cycle start date for each patient is

- the earliest start date of dosing in the Cycle X day 1 visit CRF exposure page, if the patient received study treatment on that visit (ie, any study drug with dose>0 at that visit)
- the first day of assessments in the Cycle X day 1 visit, if the patient did not receive study treatment on that visit (ie, all study drugs had dose=0 at that visit). Use start date in the exposure page if available; if start date is not available then use date of collection of vital signs on Cycle X day 1 visit.

Actual cycle end date for each patient is,

- for all cycles X except the last cycle, actual cycle end date = actual cycle (X+1) start date – 1 day
- for the last cycle, actual cycle end date = actual cycle start date + 28 – 1 day

Cycle duration (weeks) = (actual cycle end date – actual cycle start date + 1)/7

When summarizing exposure for each study drug, only cycles from first dose of study treatment until the last cycle with non-zero dose of at least one of the study drugs should be included.

Exposure may be summarized overall as dose received (cumulative dose, actual dose intensity) and as dose received relative to intended dose (relative dose intensity [RDI]).

The derivations below are provided for the following.

- Avelumab administered as a 1-hour IV infusion at a dose of 10 mg/kg once every 2 weeks in 4-week cycles
- Utomilumab administered as a 1-hour IV infusion at a dose of 20 mg, 100 mg, or 500 mg once every 4 weeks in 4-week cycles
- PF-04518600 administered as a 1-hour IV infusion at a dose of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg or 3 mg/kg once every 2 weeks in 4-week cycles
- PD 0360324 administered as a 30-min IV infusion at a dose of 50 mg, 100 mg, or 150 mg once every 2 weeks in 4-week cycles
- CMP-001 administered initially as 2 weekly 10 mg SC doses followed by IT dosing at weekly intervals for 5 additional doses of 10 mg. After the first 7 doses, CMP-001 will be administered as 10 mg IT every 2 weeks (Q2W)

6.5.3.1. Exposure to avelumab

The dose level for avelumab is calculated as actual dose administered/weight (mg/kg). The last available weight of the patient on or prior to the day of dosing will be used.

Intended duration of treatment with avelumab (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 28 – 1

Duration of exposure to avelumab (weeks) =

(last dose date of avelumab – first dose date of avelumab + 14)/7

Cumulative dose is the sum of the actual doses of avelumab received overall.

Actual Dose Intensity (DI)

- Overall actual DI (mg/kg/4-week cycle) = [overall cumulative dose (mg/kg)] / [intended duration of treatment with avelumab (weeks)/4].

Relative Dose Intensity (RDI)

- Intended DI (mg/kg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [20 (mg/kg)] / [1 (4-week cycle)] = 20 (mg/kg/4-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [20 (mg/kg/4-week cycle)]

6.5.3.2. Exposure to utomilumab

The dose level for utomilumab is calculated as actual dose administered (mg).

Intended duration of treatment with utomilumab (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 28 – 1

Duration of exposure to utomilumab (weeks) =

(last dose date of utomilumab – first dose date of utomilumab + 28)/7

Cumulative dose is the sum of the actual doses of utomilumab received overall.

Actual Dose Intensity (DI)

- Overall actual DI (mg/4-week cycle) = [overall cumulative dose (mg)] / [intended duration of treatment with utomilumab (weeks)/4]

Relative Dose Intensity (RDI)

- Intended DI (mg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [d (mg)] / [1 (4-week cycle)] = d (mg/4-week cycle)

- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [d (mg/4-week cycle)]

where d=20, 100 or 500.

6.5.3.3. Exposure to PF-04518600

The dose level for PF-04518600 is calculated as actual dose administered/weight (mg/kg). The last available weight of the patient on or prior to the day of dosing will be used.

Intended duration of treatment with PF-04518600 (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 28 – 1

Duration of exposure to PF-04518600 (weeks) =

(last dose date of PF-04518600 – first dose date of PF-04518600 + 14)/7

Cumulative dose is the sum of the actual doses of PF-04518600 received overall.

Actual Dose Intensity (DI)

- Overall actual DI (mg/kg/4-week cycle) = [overall cumulative dose (mg/kg)] / [intended duration of treatment with PF-04518600 (weeks)/4].

Relative Dose Intensity (RDI)

- Intended DI (mg/kg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [2×d (mg/kg)] / [1 (4-week cycle)] = 2×d (mg/kg/4-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [2×d (mg/kg/4-week cycle)]

where d=0.1, 0.3, 1 or 3.

6.5.3.4. Exposure to PD 0360324

The dose level for PD 0360324 is calculated as actual dose administered (mg).

Intended duration of treatment with PD 0360324 (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 28 – 1

Duration of exposure to PD 0360324 (weeks) =

(last dose date of PD 0360324 – first dose date of PD 0360324 + 14)/7

Cumulative dose is the sum of the actual doses of PD 0360324 received overall.

Actual Dose Intensity (DI)

- Overall actual DI (mg/4-week cycle) = [overall cumulative dose (mg)] / [intended duration of treatment with PD 0360324 (weeks)/4].

Relative Dose Intensity (RDI)

- Intended DI (mg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [2×d (mg)] / [1 (4-week cycle)] = 2×d (mg/4-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [2×d (mg/4-week cycle)]

where d=50, 100 or 150.

6.5.3.5. Exposure to CMP-001

The dose level for CMP-001 is calculated as actual dose administered (mg).

Intended duration of treatment with CMP-001 (weeks) =

(end date–date of first dose of study drug +1)/7,

where end date = start date of last cycle with non-zero dose of study drug + 28 – 1

Duration of exposure to CMP-001 (weeks) =

(last dose date of CMP-001 – first dose date of CMP-001 + d)/7,

where d=7 if last dose date of CMP-001 – first dose date of CMP-001 ≤39 (corresponding to the study day after the first 6 weekly doses of CMP-001, before dosing schedule changes to Q2W, plus window), or d=14 otherwise.

Cumulative dose is the sum of the actual doses of CMP-001 received overall.

Actual Dose Intensity (DI)

- Overall actual DI (mg/4-week cycle) = [overall cumulative dose (mg)] / [intended duration of treatment with CMP-001 (weeks)/4]

Relative Dose Intensity (RDI)

- Intended DI (mg/4-week cycle) = [intended cumulative dose per cycle] / [intended number of 4-weeks in a cycle] = [d (mg)] / [1 (4-week cycle)] = d (mg/4-week cycle)
- Overall RDI (%) = 100 × [overall actual DI] / [intended DI]
  = 100 × [overall actual DI] / [d (mg/4-week cycle)]

where

  - d=40 if last dose date of CMP-001 – first dose date of CMP-001 ≤25 (corresponding to Cycle 1 dosing); else

- d=30 if 26 ≤last dose date of CMP-001 – first dose date of CMP-001 ≤50 (corresponding to Cycle 2 dosing), else
- d=20

6.5.3.6. Dose reductions

Applicable only to avelumab, utomilumab, PF-04518600, PD 0360324, and CMP-001.

Dose reduction is defined as actual non-zero dose < 90% of the planned dose. The number and percentage of patients with at least one dose reduction as well as a breakdown of dose reductions (1, 2, 3, ≥4) will be summarized.

6.5.4. Concomitant medications and non-drug treatments

Combinations A and F

The following analyses will be based on the safety analysis set by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following analyses will be based on the safety analysis set by treatment group using the data from Phase1b and from Phase 2 separately and for each combination.

Concomitant medications are medications, other than study drugs, which started prior to first dose date of study treatment and continued during the on-treatment period as well as those started during the on-treatment period.

Concomitant medications will be summarized from the 'General Concomitant Medications' eCRF page.

Summary of concomitant medications will include the number and percentage of patients by Anatomical Therapeutic Chemical (ATC) Classification level 2 and preferred term. A patient will be counted only once within a given drug class and within a given drug name, even if he/she received the same medication at different times. If any concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted on decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have ATC classification level 2 coded term, it will be summarized under 'Unavailable ATC classification' category.

6.5.5. Subsequent anti-cancer therapies

Combinations A and F

The following analyses will be based on the safety analysis set by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following analyses will be based on the safety analysis set by treatment group using the data from Phase1b and from Phase 2 separately and for each combination.

Number and percentage of patients with any anti-cancer therapy after discontinuation will be tabulated overall and by type of therapy based on the data collected from the 'Follow-up Cancer Therapy', 'Follow-up Radiation Therapy' and 'Follow-up Surgery' eCRF pages.

6.6. Safety Summaries and Analyses

The Safety Analysis Set will be the primary population for safety evaluations.

Combinations A and F

The following analyses will be based on the safety analysis set by treatment group using the data from the combined Phases 1b and 2 (Cohorts A1, A2, A3 and Cohorts F1, F2, F3) and the data from Phase 2 (Cohorts A4, A5, A6, A7, A8, A9, A10).

Combinations B, C and D

The following analyses will be based on the safety analysis set by treatment group using the data from Phase1b and from Phase 2 separately and for each combination.

6.6.1. Adverse events

Treatment-emergent adverse events (TEAEs) are those events with onset dates occurring during the on-treatment period as defined in Section 3.5.1.

All analyses described will be based on TEAEs (started during the on-treatment period) if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

- **Related Adverse Events:** adverse events with relationship to study treatment (as recorded on the AE eCRF page, Relationship with study treatment = Related) reported by the investigator and those of unknown relationship (ie, no answer to the question 'Relationship with study treatment'). Related AEs are those related to any study drug (ie, at least one of the study drugs).
- **Serious Adverse Events (SAE):** serious adverse events (as recorded on the AE eCRF page, Serious Adverse Event = Yes).
- **Adverse Events Leading to Interruption of Study Treatment:** adverse events leading to interruption of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug interrupted). The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as

both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion.

- **Adverse Events Leading to Permanent Treatment Discontinuation:** adverse events leading to permanent discontinuation of study treatment (as recorded on the AE eCRF page, Action taken with study treatment = Drug withdrawn).
- **Adverse Events Leading to Death:** adverse event leading to death (as recorded on the AE eCRF page, Outcome = Fatal, as well as AEs of Grade 5).
- **Immune-related Adverse Events (irAE):** irAEs (as identified according to the methodology outlined in Appendix 1 for a pre-specified search list of MedDRA PTs, documented in the Safety Review Plan (SRP) and finalized for analysis of the current study data prior to DB lock)
- **Infusion-related Reactions (IRR)**: IRRs (as identified according to the methodology outlined in Appendix 2 for a pre-specified search list of MedDRA PTs documented in the SRP and finalized for analysis of the current study data prior to DB lock.

Unless otherwise specified, AEs will be summarized by number and percentage of patients with the AE in the category of interest as described above, by treatment group, primary SOC and PT in decreasing frequency based on the frequencies observed.

Each patient will be counted only once within each SOC or PT. If a patient experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

6.6.1.1. All adverse events

Adverse events will be summarized by worst severity (according to NCI-CTCAE version 4.03) per patient, using the latest version of MedDRA preferred term (PT) as event category and MedDRA primary system organ class (SOC) body term as Body System category.

In case a patient has events with missing and non-missing grades, the maximum of the non-missing grades will be displayed. No imputation of missing grades will be performed.

The following tables will be created:

- The overall summary of AEs table will include the frequency (number and percentage) of patients with each of the following by treatment group:
  - TEAEs
  - TEAEs, Grade ≥ 3
  - Related TEAEs
  - Related TEAEs, Grade ≥ 3
  - TEAEs leading to interruption of any study drug
  - TEAEs leading to discontinuation of avelumab

- TEAEs leading to discontinuation of utomilumab
- TEAEs leading to discontinuation of PF-04518600
- TEAEs leading to discontinuation of PD 0360324
- TEAEs leading to discontinuation of CMP-001
- TEAEs leading to discontinuation of any study drug
- Related TEAEs leading to discontinuation of avelumab
- Related TEAEs leading to discontinuation of utomilumab
- Related TEAEs leading to discontinuation of PF-04518600
- Related TEAEs leading to discontinuation of PD 0360324
- Related TEAEs leading to discontinuation of CMP-001
- Related TEAEs leading to discontinuation of any study drug
- Serious TEAEs
- Related Serious TEAEs
- TEAEs leading to death
- Related TEAEs leading to death
- irAEs
- IRRs
- Cytokine Release Syndrome (Combination F only)

- TEAEs by SOC and PT and worst grade
- TEAEs related to any study drug by SOC and PT and worst grade
- TEAEs leading to death by SOC and PT
- Related TEAEs leading to death by SOC and PT

6.6.1.2. Adverse events leading to interruption of study treatment

The eCRF does not allow for a clear separation between interruption of an infusion and delays of administration for a parenteral drug as both are recorded using the same term on the eCRF ("Drug interrupted"). IRRs will be excluded in the analysis of AEs leading to Drug Interruption in case they only led to an interruption of the infusion (ie, did not lead to a dose reduction or a dose delay).

As such, AEs leading to interruption will be defined as AEs identified in the AE eCRF page with an action taken with study treatment of 'drug interrupted' excluding

- IRRs that occurred on the day of infusion with ≥90% of the planned dose given (ie IRRs that did not lead to a dose reduction) and subsequent administration of study drug had no delay (as defined in Section 6.5.3.6). These IRRs will be considered as IRRs leading to interruption of infusion.
- IRRs occurring on the day after infusion and subsequent dose administration had no delay (as defined in Section 6.5.3.6).

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to interruption of each study drug by treatment group:

- TEAEs leading to interruption of avelumab by SOC and PT
- TEAEs leading to interruption of utomilumab by SOC and PT
- TEAEs leading to interruption of PF-04518600 by SOC and PT
- TEAEs leading to interruption of PD 0360324 by SOC and PT

The listing of all AEs leading to interruption of study treatment will also be provided with the relevant information.

6.6.1.3. Adverse events leading to discontinuation of study treatment

The frequency (number and percentage) of patients with each of the following will be presented for TEAEs leading to permanent discontinuation of each study drug and study treatment, by treatment group:

- TEAEs leading to discontinuation of avelumab by SOC and PT
- TEAEs leading to discontinuation of utomilumab by SOC and PT
- TEAEs leading to discontinuation of PF-04518600 by SOC and PT
- TEAEs leading to discontinuation of PD 0360324 by SOC and PT
- TEAEs leading to discontinuation of CMP-001 by SOC and PT
- TEAEs leading to discontinuation of any study drug by SOC and PT
- Related TEAEs leading to discontinuation of avelumab by SOC and PT
- Related TEAEs leading to discontinuation of utomilumab by SOC and PT
- Related TEAEs leading to discontinuation of PF-04518600 by SOC and PT
- Related TEAEs leading to discontinuation of PD 0360324 by SOC and PT
- Related TEAEs leading to discontinuation of CMP-001 by SOC and PT
- Related TEAEs leading to discontinuation of any study drug by SOC and PT

The listing of all AEs leading to treatment discontinuation will also be provided with the relevant information.

6.6.2. Deaths

The frequency (number and percentage) of patients in the safety analysis set who died and who died within 30 days after last dose of study treatment as well as the reason for death, will be tabulated based on information from the 'Notice of Death' and 'Survival Follow-Up' eCRFs, by treatment group.

- All deaths
- Deaths within 30 days after last dose of study treatment
- Reason for Death
  - Disease progression
  - Study treatment toxicity
  - AE not related to study treatment
  - Unknown
  - Other.

In addition, date and cause of death will be provided in individual patient data listing together with selected dosing information (study treatment received, date of first / last administration, dose) and will include the following information:

- AEs with fatal outcome (list preferred terms of AEs with outcome=Fatal, as well as AEs of Grade 5),
- Flag for death within 30 days of last dose of study treatment.

6.6.3. Serious adverse events

The frequency (number and percentage) of patients with each of the following will be presented for treatment-emergent SAEs by treatment group:

- SAEs by SOC and PT
- Related SAEs by SOC and PT

The listings of all SAEs will also be provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

6.6.4. Other significant adverse events

The frequency (number and percentage) of patients with each of the following will be presented for irAEs, by treatment group:

- irAEs, by Cluster, PT, and maximum CTCAE Grade
- irAEs leading to discontinuation of avelumab, by Cluster and PT
- irAEs leading to discontinuation of any study drug by Cluster and PT
- Serious irAEs, by Cluster and PT

The listing of all irAEs will also be provided with the relevant information with a flag for irAEs with onset outside of the on-treatment period.

The frequency (number and percentage) of patients with each of the following will be presented for IRRs, by treatment group and for each study drug:

- IRRs, by PT and maximum CTCAE grade
- IRRs leading to discontinuation of avelumab, by PT
- IRRs leading to discontinuation of any study drug, by PT
- Serious IRRs, by PT
- Time related to first onset of an IRR (infusion 1, infusion 2, infusion 3, infusion 4 or later). For IV study drugs administered in combination the infusion numbers are those associated with the regimen, rather than the individual study drugs.

The listing of all IRRs will also be provided with the relevant information with a flag for IRRs with onset outside of the on-treatment period.

For Combination F only (Cohorts F1, F2 and F3) Cytokine Release Syndrome (as defined in the SRP) may be summarized and listed as described above for irAEs by Cluster and PT or by PT only, as applicable.

6.6.5. Laboratory data

6.6.5.1. Hematology and chemistry parameters

Laboratory results will be classified according to the NCI-CTCAE criteria version 4.03. Non-numerical qualifiers (with the exception of fasting flags) will not be taken into consideration in the derivation of CTCAE criteria (eg, hypokalemia Grade 1 and Grade 2 are only distinguished by a non-numerical qualifier and therefore Grade 2 will not be derived). Additional laboratory results that are not part of NCI-CTCAE will be presented according to the categories: below normal limit, within normal limits and above normal limit (according to the laboratory normal ranges).

Abnormalities classified according to NCI-CTCAE toxicity grading v.4.03 will be described using the worst grade. For those parameters which are graded with two toxicities such as potassium (hypokalemia/hyperkalemia), the toxicities will be summarized separately. Low direction toxicity (eg, hypokalemia) grades at baseline and post baseline will be set to 0 when the variables are derived for summarizing high direction toxicity (eg, hyperkalemia), and vice versa.

For **WBC differential counts** (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), the absolute value will be used when reported. When only percentages are available (this is mainly important for neutrophils and lymphocytes, because the CTCAE grading is based on the absolute counts), the absolute value is derived as follows:

$$\text{Derived differential absolute count} = (\text{WBC count}) \times (\text{Differential \%value} / 100)$$

If the range for the differential absolute count is not available (only range for value in % is available) then Grade 1 will be attributed to as follows:

- Lymphocyte count decreased:
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 800/mm3
- Neutrophil count decreased
  - derived absolute count does not meet Grade 2-4 criteria, and
  - % value < % LLN value, and
  - derived absolute count ≥ 1500/mm3

For **calcium**, CTCAE grading is based on Corrected Calcium and Ionized Calcium (CALCIO). Corrected Calcium is calculated from Albumin and Calcium as follows

Corrected calcium (mmol/L) = measured total Calcium (mmol/L) + 0.02 (40 - serum albumin [g/L])

Liver function tests: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBILI) are used to assess possible drug induced liver toxicity. The ratios of test result over upper limit of normal (ULN) will be calculated and classified for these three parameters during the on-treatment period.

Summary of liver function tests will include the following categories. The number and percentage of patients with each of the following during the on-treatment period will be summarized by treatment group:

- ALT ≥ 3×ULN, ALT ≥ 5×ULN, ALT ≥ 10×ULN, ALT ≥ 20×ULN
- AST ≥ 3×ULN, AST ≥ 5×ULN, AST ≥ 10×ULN, AST ≥ 20×ULN
- (ALT or AST) ≥ 3×ULN, (ALT or AST) ≥ 5×ULN, (ALT or AST) ≥ 10×ULN, (ALT or AST) ≥ 20×ULN
- TBILI ≥ 2×ULN
- Concurrent ALT ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent AST ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and ALP > 2×ULN
- Concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing)

Concurrent measurements are those occurring on the same date.

Categories will be cumulative, ie, a patient with an elevation of AST ≥10×ULN will also appear in the categories ≥5×ULN and ≥3×ULN. Liver function elevation and possible Hy's Law cases will be summarized using frequency counts and percentages.

An evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot will also be created, with different symbols for different treatment groups, by graphically displaying

- peak serum ALT(/ULN) vs peak total bilirubin (/ULN) including reference lines at ALT=3×ULN and total bilirubin =2×ULN.
- peak serum AST(/ULN) vs peak total bilirubin (/ULN) including reference lines at AST=3×ULN and total bilirubin =2×ULN .

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with concurrent (ALT or AST) ≥ 3×ULN and TBILI ≥ 2×ULN and (ALP ≤ 2×ULN or missing) will be provided.

Parameters with NCI-CTC grades available:

The laboratory toxicities will be tabulated using descriptive statistics (number of patients and percentages) during the on-treatment period. The denominator to calculate percentages for each laboratory parameter is the number of patients evaluable for CTCAE grading (ie those patients for whom a Grade 0, 1, 2, 3 or 4 can be derived).

- The shift table will summarize baseline CTCAE grade versus the worst on-treatment CTCAE grade. The highest CTCAE grade during the on-treatment period is considered as the worst grade for the summary.
- The number and percentage of patients with newly occurring or worsening laboratory abnormalities during the on-treatment period will be summarized by worst grade on-treatment (Grade 1, 2, 3, 4, Grade 3/4 and any grade (Grades 1-4)).

The above analyses apply to hematology and chemistry evaluations which can be graded per CTCAE, ie:

- Hematology:

  Hemoglobin (HB), Leukocytes (white blood cell decreased), Lymphocytes (lymphocyte count increased/decreased), Neutrophils / Absolute Neutrophils Count (ANC) (neutrophil count decreased), Platelet Count (PLT) (platelet count decreased).

- Serum Chemistry:

  Albumin (hypoalbuminemia), Alkaline Phosphatase (alkaline phosphatase increased), Alanine Aminotransferase (ALT) (ALT increased), Amylase (serum amylase increased), Aspartate Aminotransferase (AST) (AST increased), Total Bilirubin (blood bilirubin increased, Creatinine (creatinine increased), Creatine Kinase (CPK increased), Potassium (hypokalemia/ hyperkalemia), Sodium (hyponatremia/ hypernatremia), Magnesium (hypomagnesemia/hypermagnesemia), Calcium (hypocalcemia/ hypercalcemia), Glucose (hypoglycemia/hyperglycemia), Gamma Glutamyl Transferase (GGT) (GGT increased), Lipase (lipase increased), Phosphates (hypophosphatemia).

Parameters with NCI-CTC grades not available:

Hematology and chemistry evaluations which cannot be graded per CTCAE criteria will be summarized as frequency (number and percentage) of patients with:

- shifts from baseline normal to at least one result above normal during on-treatment period
- shifts from baseline normal to at least one result below normal during on-treatment period

In this study, these apply to the following parameters:

- Hematology: Absolute Monocytes, Absolute Eosinophils, Absolute Basophils
- Serum Chemistry: Chloride, Total Urea, Uric Acid, Total Protein, C-Reactive Protein, Lactate Dehydrogenase (LDH)

6.6.5.2. Other laboratory parameters

The listings of laboratory results will be provided for all laboratory parameters. The listings will be sorted by parameters and assessment dates or visits for each patient. Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

6.6.6. Vital signs

Weight for the purposes of dose calculation will be recorded at screening and within 3 days pre-dose Day 1 of each cycle. Height will be measured at screening only.

6.6.7. Electrocardiogram

ECG summaries will include all ECG assessments from the on-treatment period. QTcB and QTcF will be derived based on RR and QT (see below). The average of the replicate measurements should be determined after the derivation of the individual parameter at each time point.

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds, and can be estimated as 60/Heart Rate.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions. Data will be summarized using QTcF and QTcB.

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc) by treatment group, during the on-treatment period. The denominator to calculate percentages for each category is the number of patients evaluable for the category.

- Pearson correlation between QT and HR, QTc (QTcB and QTcF) and HR using individual (non-averaged) baseline assessments
- Frequency (number and percentage) of patients with notable ECG values according to the following categories:
  - QT/QTc increase from baseline >30 ms, >60 ms
  - QT/QTc > 450 ms, > 480 ms, > 500 ms
  - HR ≤ 50 bpm and decrease from baseline ≥ 20 bpm
  - HR ≥ 120 bpm and increase from baseline ≥ 20 bpm
  - PR ≥ 220 ms and increase from baseline ≥ 20 ms
  - QRS ≥ 120 ms

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the shift table analysis of notable QT parameters.

7. INTERIM ANALYSES

There is no formal interim analysis planned for this study.

8. REFERENCES

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5. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 53: 457-81, 1958.

9. APPENDICES

Appendix 1. Immune-Related Adverse Events

The MedDRA PTs and clusters for irAEs are defined in the Safety Review Plan (SRP) for avelumab.

Immune-related AEs (irAEs) will be programmatically identified as outlined in Table 15. This case definition is hierarchical, ie, each step is only checked for patients and events that have already met the prior step.

Table 15. Case Definition for irAEs

Step	Selection Criteria	Additional Notes
1	Event selected based on a list of pre-specified MedDRA PTs within clusters. These are included in the SRP as Tier1 events (Immune-mediated xxxx). If AE matches the list, then it is in for the next step	
2	AE onset during 1st study drug administration or anytime thereafter through 90 days after last dose of study treatment.	This is regardless of start of new anti-cancer drug therapy and regardless of TEAE classifications
3	Answer in the AE eCRF page to 'Was another treatment given because of the occurrence of the event' is 'YES'	Steps 3 and 4 will be checked concurrently. Step 5 will be checked if the criteria in Step 4 is met, irrespective of whether the Criteria in Step 3 is met.
4	AE treated with corticosteroids or other immunosuppressant therapy. For endocrinopathies only: AE required hormone replacement	Look in the conmed pages for AE identifiers that match the AEs from Step 3. For each of such AEs if A) OR B) OR C) below are met then the AE is in for the next step A) conmed ATC code is in (H02A, H02B, D07, A01AC, S01BA, S01BB, L04AA, L04AB, L04AC, L04AD, L04AX, A07EA) and AE PT is in any of the irAE clusters. B) conmed ATC code is in (H03A, H03B) and AE PT is in one of the irAE clusters associated with "Immune-mediated endocrinopathies" C) conmed ATC code is A10A and AE PT is in the irAE cluster associated with "Immune-mediated endocrinopathies: Type I Diabetes Mellitus"

5	A) No clear etiology (other than immune mediated etiology) B) Histopathology / biopsy consistent with immune-mediated event Event is in if [Answer to 5B1 and 5B2 is YES (regardless of answer to 5A)] OR [Answer to 5B1 is YES AND answer to 5B2 is NO AND answer to 5A is NO] OR [Answer to 5B1 is NO AND answer to 5A is NO]	A) From the AE eCRF page. Is the AE clearly related to an etiology other than immune-mediated etiology? Yes / No If answer is Yes, check all that apply: • Underlying malignancy / progressive disease. • Other medical conditions. • Prior or concomitant medications / procedures. • Other. Specify. B) From the AE eCRF page. B1) Was there a pathology /histology evaluation performed to investigate the AE? Y/N B2) If answer to the above is Yes, does the pathology/histology evaluation confirms an immune mediated mechanism for the AE? Y/N B3) If pathology / histology evaluation performed to investigate the AE, provide summary of relevant findings of the pathology /histology report. (Free Text)

The data set associated with irAEs may be refined based on medical review. The final data set including any changes based on medical review (eg, addition of cases that are not selected by the programmatic algorithm) will be the basis of the irAE analyses.

Appendix 2. Infusion Related Reactions

For defining an AE as IRR, the onset of the event in relation to the infusion of study drug and time to resolution of the event will be considered.

- All AEs identified by the MedDRA PT query describing signs and symptoms will be considered potential IRRs when onset is on the day of study drug infusion (during or after infusion) and the event resolved with end date within 2 days after onset.
- All AEs identified by the MedDRA PTs of Infusion related reaction, Drug hypersensitivity, Anaphylactic reaction, Hypersensitivity, Type 1 hypersensitivity, will be considered potential IRRs when onset is on the day of study drug infusion (during or after the infusion) or the day after the study drug infusion (irrespective of resolution date).

The list of MedDRA PTs for 'IRRs SIGNS and SYMPTOMS' and PTs 'IRRs CORE' are defined in the SRP for avelumab.

Infusion-related reactions (IRRs) will be programmatically identified as outlined in Table 16 or Table 17 and will be identified for IV drugs only.

Table 16. Case Definition for IRRs – IV Study Drugs Administered Alone Or In Combination With Non-IV Study Drugs

Condition	Selection criterion
If AE meets [1 AND 2] OR [3 AND (4A OR 4B)] then AE is classified as an IRR	
1	PT is included in the 'IRRs SIGNS and SYMPTOMS' list
2	• AE onset date = date of infusion of study drug AND • AE timing related to study drug ('DURING', 'AFTER') AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date ≤2
3	PT is included in the 'IRRs CORE' list
4A	• AE onset date = date of infusion of study drug AND • AE timing related to study drug in ('DURING', 'AFTER')
4B	AE onset on the day after infusion

Table 17. Case Definition for IRRs – IV Study Drugs Administered in Combination (eg, Doublets or Triplets)

Condition	Selection criterion
IRR can be associated with the first IV drug and/or subsequent IV drugs that are administered in combination. Without loss of generality assume triplet IV with D_1 administered first then D_2 then D_3. The IV study drug or drugs associated with the IRR need to be identified in the analysis data set to enable subsequent analysis. The following are not sequential and an AE can be classified as an IRR associated with multiple D_J from one or more of I, II, III, IV, V below: I - If the AE meets [1 AND 2A1] for a D_J then the AE is classified as an IRR associated with the D_J that meets the 2A1 criterion II - If the AE meets [1 AND 2A2] for a D_J then the AE is classified as an IRR associated with the D_J and associated with D_{J+1} that meets the 2A2 criterion III - If the AE meets [3 AND 4B] for any D_J then the AE is classified as an IRR associated with all D_J that meet the 4B criterion. IV- If the AE meets [3 AND 4A1] for a D_J then the AE is classified as an IRR associated with the D_J that meets the 4A1 criterion V- If the AE meets [3 AND 4A2] for a D_J then the AE is classified as an IRR associated with the D_J and associated with D_{J+1} that meets the 4A2 criterion	
1	PT is included in the 'IRRs SIGNS and SYMPTOMS' list
2A1	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • [AE timing related to study drug D_{J+1} ('BEFORE') OR AE onset date < date of infusion of study drug D_{J+1}]AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date ≤2
2A2	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • AE timing related to study drug D_{J+1} ('DURING', 'AFTER') AND • AE outcome in ('RECOVERED/RESOLVED', 'RECOVERED/RESOLVED WITH SEQUELAE', 'RECOVERING/RESOLVING') AND • AE end date – AE onset date ≤2
3	PT is included in the 'IRRs CORE' list
4A1	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • [AE timing related to study drug D_{J+1} ('BEFORE') OR AE onset date < date of infusion of study drug D_{J+1}]
4A2	• AE onset date = date of infusion of study drug D_J AND • AE timing related to study drug D_J ('DURING', 'AFTER') AND • AE timing related to study drug D_{J+1} ('DURING', 'AFTER')
4B	AE onset on the day after infusion of study drug D_J