STATISTICAL ANALYSIS PLAN

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A Phase 1/2, Open-label Study Investigating the Safety, Tolerability and Efficacy of ASP7517 as a Single Agent and in Combination with Pembrolizumab in Patients with Advanced Solid Tumors Known to Express WT1 Antigen

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I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
aAVC	artificial adjuvant vector cell
AE	adverse event
AEsi	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APGD	Astellas Pharma Global Development
ASCM	analysis set classification meeting
ATC	anatomical therapeutic chemical
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
BOIN	Bayesian optimal interval
BOP2	Bayesian optimal phase 2
CI	confidence interval
C_{max}	maximum concentration
CR	complete response
CRC	colorectal cancer
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	concentration immediately prior to dosing at multiple dosing
DCR	disease control rate per RECIST v1.1
DEAS	DLT evaluation analysis set
DESC	dose escalation and safety committee
DBP	diastolic blood pressure
DLT	dose limiting toxicity
DOR	duration of response per RECIST v1.1
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISpot	enzyme-linked immunospot
EOT	end of treatment
FAS	full analysis set
ICH	International Conference on Harmonization
iCR	complete response per iRECIST
iDCR	disease control rate per iRECIST
iDOR	duration of response per iRECIST
INR	international normalize ratio
iORR	objective response rate per iRECIST
IP	investigational product
iPFS	progression-free survival per iRECIST
iPR	partial response per iRECIST
irAE	immune-related adverse event

Abbreviations	Description of abbreviations
iRECIST	immune response evaluation criteria in solid tumors
IRR	infusion related reactions
iSD	stable disease per iRECIST
iUPD	unconfirmed disease progression per iRECIST
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response rate per RECIST v1.1
OS	overall survival
PD	progressive disease
PDAS	pharmacodynamics analysis set
PKAS	pharmacokinetic analysis set
PR	partial response per RECIST v1.1
PS	performance status
PT	preferred term
QT	Q-T interval from electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	Fridericia-corrected QT interval
RAS	response analysis set
RBC	red blood cell
RCL	replication competent lentivirus
RDI	relative dose intensity
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SBP	systolic blood pressure
SD	stable disease
SOC	system organ class
TBL	total bilirubin
TEAE	treatment emergent adverse event
TLF	tables, listings and figures
t_{max}	time to maximum concentration
ULN	upper limit of normal
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

List of Key Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
End of Study	This date reflects when a participant completes follow-up.
Enroll	To register or enter into a clinical trial. NOTE: Once a participant has been enrolled, the clinical trial protocol applies to the participant.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a participant, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screen failure	Potential participant who did not meet 1 or more criteria required for participation in a trial.
Screening	A process of active consideration of potential participants for enrollment in a trial.
Screening period	Period of time before entering the investigational period, usually from the time of starting a participant signing consent until just before the test drug or comparative drug (sometimes without randomization) is given to a participant.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes procedures for executing the statistical analysis to fulfill the objectives of the study.

The final SAP will be approved prior to database hardlock.

Changes to the planned analyses in the final SAP that impact the statistical analyses will be documented in the Clinical Study Report (CSR).

2 TREATMENT PROTOCOL OBJECTIVES AND DESIGN

2.1 Study Objectives

Objectives	**Endpoints**
Primary	
• To evaluate the safety and tolerability of ASP7517 when administered as a single agent and in combination with pembrolizumab	• Safety and tolerability as noted by: DLTs, AEs, SAEs, laboratory test results (serum, chemistry, hematology, coagulation and urinalysis, pregnancy test), ECGs, vital signs, physical exams and ECOG performance status scores
• To determine the RP2D and/or the MTD of ASP7517 when administered as a single agent and in combination with pembrolizumab (phase 1)	• DLTs
• To evaluate the clinical response of ASP7517 when administered as a single agent and in combination with pembrolizumab (phase 2)	• Objective response rate per iRECIST (iORR) by independent central review[(1)]
Secondary	
• To evaluate other measures of anticancer activity of ASP7517 when administered as a single agent and in combination with pembrolizumab based on central and local assessment	• Objective response rate per RECIST v1.1(ORR) • Disease control rate per iRECIST (iDCR) and RECIST v1.1 (DCR) • Progression-free survival per iRECIST (iPFS) and RECIST v1.1 (PFS) • Overall survival (OS) • Duration of response per iRECIST (iDOR) and RECIST v1.1 (DOR)

Objectives	Endpoints
Exploratory	
● To evaluate potential genomic, proteomic and/or other biomarkers that may correlate with treatment outcome when ASP7517 administered as a single agent and in combination with pembrolizumab	● Exploratory tumor and peripheral biomarkers that may correlate with treatment outcome of ASP7517 monotherapy or in combination with pembrolizumab
● To evaluate pharmacodynamic activities of ASP7517 as a single agent and in combination with pembrolizumab	● Pharmacodynamic effects of ASP7517 as a monotherapy or in combination with pembrolizumab, such as changes in: o Cytokine expression and secretion (e.g., IFNg) o WT1-specific T lymphocytes (e.g., cytotoxic T lymphocytes) o Immune cell populations (NKT cells, NK cells, etc.) o Anti-WT1 antibodies o Tumor microenvironment
● To characterize the pharmacokinetic profile of ASP7517 when administered as a monotherapy and in combination with pembrolizumab	● Cellular DNA load and kinetic parameter estimates (including AUC, C_{max}, C_{trough} and t_{max}) for ASP7517 as a monotherapy or in combination with pembrolizumab

AE: adverse event; DLT: dose limiting toxicity; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; IFNg: interferon gamma; iRECIST: immune response evaluation criteria in solid tumors; MTD: maximum tolerated dose; NK: natural killer; NKT: natural killer T; RECIST: response evaluation criteria in solid tumors; RP2D: recommended phase 2 dose; SAE: serious adverse event; WT1: Wilms' tumor protein 1.
(1) There will be no Independent Central Review data.

2.2 Study Design

This study is a phase 1/2, open-label study of ASP7517 as monotherapy and in combination with pembrolizumab in selected patients with advanced solid tumors known to express WT1 antigen.

This study consists of arms receiving ASP7517 monotherapy and arms receiving ASP7517 and pembrolizumab combination therapy in phase 1 (dose escalation cohort) and phase 2 (dose expansion cohort).

Additional cohorts may be added by a protocol amendment to further evaluate ASP7517 as a single agent and/or in combination with another anti-cancer agent.

For participants in all arms/phases, the study consists of the following periods:

- Screening: (up to 28 days)
- Treatment (up to six 28-day cycles):
    - ASP7517 Monotherapy Arm: ASP7517 every 28 days

  - ASP7517 and Pembrolizumab Combination Therapy Arm: ASP7517 every 28 days and pembrolizumab every 6 weeks in combination (up to 6 doses of ASP7517 in combination with a total of 4 doses of pembrolizumab);

- End of Treatment (EOT) Visit: Participants will complete an EOT visit within 7 days of EOT determination or prior to initiation of new anticancer therapy
- Safety Follow-up: Participants will complete 30-day, 60-day and 90-day safety follow-up visits from the last dose of study drug or prior to the initiation of new anticancer therapy
- Observation Period.
  - Observation Period for Monotherapy: All participants will enter an observation period after EOT, except those with iCPD, iUPD (per independent central review or local review) and who are not clinically stable or clinical progression is confirmed by the investigator. The observation period consists of safety follow-up visits (30, 60 and 90 days after last dose administered in the treatment period) and visits for only tumor imaging (every 8 weeks for up to 48 weeks).
  - Observation Period for Combination Therapy: Participants will enter an observation period 6 weeks from the last dose of pembrolizumab in combination with ASP7517 (up to 78 weeks and may receive pembrolizumab monotherapy up to 13 doses every 6 weeks for qualifying participants)
- Survival Follow-up: Telephone contact will be made every 3 months for up to 12 months

Details of the schedule of clinical assessments are available in the protocol.

Phase 1 Dose Escalation Cohort for Monotherapy and Combination Therapy Arms

The monotherapy and combination therapy dose escalation portion will evaluate escalating dose levels of ASP7517 in approximately 9 to 12 dose limiting toxicity (DLT)-evaluable participants.

Phase 2 Monotherapy Arm Dose Expansion Cohort

Monotherapy dose expansion will be opened after the phase 1 monotherapy arm dose escalation cohort has been completed. If a confirmed response (partial response based on iRECIST [iPR] or complete response based on iRECIST [iCR], per independent central review) occurs in a monotherapy arm dose escalation cohort (for melanoma, ovarian cancer and CRC only), a tumor-specific dose expansion cohort may be opened in that tumor type, at the dose level in which the confirmed response was observed and phase 1 dose escalation has been completed. Once RP2D is determined, the melanoma expansion cohort may be opened (if not already opened due to an observed response in a dose escalation cohort). Participants with CPI refractory metastatic melanoma will be enrolled in the monotherapy dose escalation or expansion cohorts to allow for enrollment of this patient population in the combination

arm dose expansion cohort. If antitumor activity was observed in dose escalation or melanoma dose expansion stage 1, expansion cohorts for CRC and ovarian cancer may be opened. If a confirmed response (PR based on iRECIST [iPR] or a CR based on iRECIST [iCR], per independent central review) occurs in a monotherapy arm dose escalation cohort for any other tumor type, a tumor-specific dose expansion cohort may be opened in that tumor type at the dose level in which the confirmed response was observed and phase 1 dose escalation has been completed.

Objective response rate per iRECIST (iORR), as confirmed per independent central review, is monitored using the Bayesian optimal phase 2 (BOP2) design [Zhou et al, 2017]. The number of dose levels investigated during phase 2 will be based upon the data from phase 1. If the iORR does not meet the optimal stopping boundaries after stage 1 (detailed in section 6.9), then additional participants may be enrolled for that tumor type at each dose level (stage 2). Otherwise, the enrollment at that dose level will be closed.

Phase 2 Combination Therapy Arm Dose Expansion Cohort

The combination therapy arm dose expansion cohort will be opened after the phase 1 dose escalation cohort has been completed. The metastatic melanoma CPI naïve cohort will be open. If 5 confirmed responses (iPR or iCR per independent central review) are observed in metastatic melanoma CPI naïve participants, expansion cohorts for CRC, ovarian cancer, and metastatic melanoma CPI refractory may be opened. In addition, if a confirmed response (iPR or iCR per independent central review) is observed in metastatic melanoma CPI refractory participants in the monotherapy arm, an expansion cohort for melanoma refractory participants may be opened for combination arm therapy, if not yet opened.

As in all cohorts, if the iORR per independent central review does not meet the optimal stopping boundaries after stage 1(see section 6.9) for metastatic melanoma CPI naïve participants, then additional participants may be enrolled up to the maximum total sample size for that tumor type.

Similarly, for all other tumor types, if the iORR per independent central review does not meet the optimal stopping boundaries for that tumor type after stage 1 (see section 6.9) , then additional participants may be enrolled up to the total maximum sample size at each dose level.

If both monotherapy and combination therapy arms in the expansion cohorts are open for the same tumor type, randomization will be expanded to include both monotherapy and combination therapy arms and the randomization ratio will be based on the number of open slots still available at each dose level.

Replacement of Participants in Phase 2 Dose Expansion Cohort

If a participant in a phase 2 dose expansion cohort is not response evaluable (defined as the response analysis set [RAS]), an additional participant may be enrolled in that cohort based on sponsor discretion.

2.3 Randomization

Priority for enrollment will be given to the phase 1 dose escalation portion before the phase 2 dose expansion.

In case the enrollment for both monotherapy escalation arm and combination therapy escalation arm opens together, participants will be randomized to either monotherapy or combination arm in 1:1 ratio.

For phase 2 enrollment, if more than 1 dose level is open for enrollment within a selected disease type, the newly enrolled participants with that disease type will be randomly allocated to 1 of the open dose levels. Randomization will be weighted towards newly opened dose levels, with the allocation ratio based on the number of open slots still available at each dose level. For example, if dose level 'x' enrolled 3 participants and dose level 'y' is newly opened for expansion of ASP7517 monotherapy for melanoma, the next participant would be randomly allocated to dose level 'x' or 'y' with the ratio of 15:18.

If both monotherapy and combination therapy expansion arms are open for the same tumor type, randomization will be expanded to include both monotherapy and combination therapy arms and the randomization ratio will be based on the number of open slots still available at each dose level.

3 SAMPLE SIZE

Phase 1 Dose Escalation:

The sample size of approximately 24, including 12 from monotherapy and 12 from combination therapy, is not based on a statistical power calculation. The number of participants enrolled will be dependent on the DLT incidence. The estimated number of participants should provide adequate information for the dose escalation and safety objectives of the study.

Phase 2 Dose Expansion:

It is estimated that up to approximately 361 participants may be enrolled in the monotherapy and combination therapy arms (approximately 129 participants for monotherapy and 232 participants for combination therapy). The iORR is monitored using the BOP2 design. For each indication, with assumptions mentioned in the Statistical Hypotheses below, the statistical power would be approximately 0.80 while controlling the type I error rate at 0.05 (1-sided).

Monotherapy

Statistical Hypotheses:

H0: iORR is 10%, under which the treatment is deemed as unacceptable.

H1: iORR is at least 25%, under which the treatment is deemed as acceptable.

Combination Therapy

Statistical Hypotheses:

Metastatic Melanoma CPI Naïve

H0: iORR is 25%, under which the treatment is deemed as unacceptable.

H1: iORR is at least 40%, under which the treatment is deemed as acceptable.

Metastatic Melanoma CPI Refractory

H0: iORR is13%, under which the treatment is deemed as unacceptable.

H1: iORR is at least 28%, under which the treatment is deemed as acceptable.

Ovarian Cancer

H0: iORR is 15%, under which the treatment is deemed as unacceptable.

H1: iORR is at least 30%, under which the treatment is deemed as acceptable.

Colorectal Cancer

H0: iORR is 18%, under which the treatment is deemed as unacceptable.

H1: iORR is at least 33%, under which the treatment is deemed as acceptable.

4 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses. Full Analysis Set (FAS) and Response Analysis Set (RAS) will be used for efficacy analysis. Safety Analysis Set (SAF) will be used for the analyses of safety variables. Pharmacokinetic Analysis Set (PKAS) will be used for pharmacokinetic analyses. The biomarker pharmacodynamics analysis set (PDAS) will be used for all analyses of pharmacodynamics data. The data from all participants who were enrolled in the study will be included in the data listings. All enrolled participants are those who signed the informed consent form and were assigned a subject number.

For each dose level group, the number and percentage of participants will be characterized for all treated participants and by each analysis set.

Population	**Description**
Enrolled	All participants who sign the informed consent form are allocated to treatment.
Full Analysis Set (FAS)	All participants who are enrolled and receive at least one dose of study treatment.
Response Analysis Set (RAS)	The response analysis set will consist of all participants who are enrolled and receive at least 1 dose of IP and have at least 1 post baseline primary efficacy measurement.
Safety Analysis Set (SAF)	All participants who take at least 1 dose of IP.

Pharmacokinetic Analysis Set (PKAS)	The PKAS consists of the administered population for which pharmacokinetics data are available for at least 1 time point. Additional participants may be excluded from the PKAS at the discretion of the pharmacokineticist.
Pharmacodynamic Analysis Set (PDAS)	The PDAS will include the participants from the administered population for whom sufficient pharmacodynamic measurements were collected. The PDAS will be used for all analyses of pharmacodynamic data.
DLT Evaluation Analysis Set (DEAS)	The DEAS is defined as all participants in SAF excluding participants who meet any of the following criteria: • Participant is discovered to have enrolled without fully satisfying eligibility criteria. • Participant received less than the planned dose in cycle 1 for reasons other than DLT. • Participant has no DLT and withdraws from the study before the end of DLT evaluation period. The DEAS will be used for the analysis of DLT data.

5 ENDPOINTS

5.1 Efficacy Endpoints

Tumor-related efficacy variables are evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and guidelines for response criteria for use in trials testing immunotherapeutics (iRECIST) (Seymour, L., et al., 2017).

5.1.1 Primary Efficacy Endpoints

Due to study's early closure, independent central review data will not be collected; investigator assessed endpoints will be presented.

5.1.1.1 Objective Response Rate per iRECIST (iORR)

iORR is defined as the proportion of participants for each dose level whose best overall response is rated as confirmed iCR or iPR per iRECIST. Endpoints will include:

- iORR with confirmed response by investigator assessment
- iORR with unconfirmed response by investigator assessment

5.1.2 Secondary Efficacy Endpoints

5.1.2.1 Objective Response Rate per RECIST (ORR)

ORR is defined as the proportion of participants for each dose level whose best overall response is rated as CR or PR per RECIST v1.1 for the endpoints of:

- ORR with confirmed response by investigator assessment
- ORR with unconfirmed response by investigator assessment

5.1.2.2 Disease Control Rate per iRECIST (iDCR)

iDCR is defined as the proportion of participants for each dose level whose best overall response is rated as confirmed iCR, iPR or stable disease (iSD) per iRECIST.

5.1.2.3 Disease Control Rate per RECIST v1.1 (DCR)

DCR is defined as the proportion of participants for each dose level whose best overall response is rated as confirmed CR, PR or SD per RECIST v1.1.

5.1.2.4 Overall Survival (OS)

OS is defined as the time from the date of first dose until the date of death from any cause (death date – first dose date + 1). For a participant who is not known to have died by the end of study follow-up, OS is censored at the date of last contact (date of last contact – first dose date + 1).

Table 1 OS Definition

Situation	Date of Event or Censor	Outcome
Death before or on analysis cutoff date	Date of death	Event
Death after analysis cutoff date	Analysis cutoff date	Censor
Last known alive is before or on cutoff date	Last known alive date	Censor
Last known alive is after cutoff date	Analysis cutoff date	Censor

OS = Date of Event or Censor – Date of First Dose +1

5.1.2.5 Progression-free Survival per iRECIST (iPFS)

iPFS is defined as the time from the start of the study treatment until death from any cause or radiographic disease progression assessed per iRECIST by investigator assessment, whichever occurs first.

If iUPD occurs but iSD, iPR, or iCR is observed any time subsequent to iUPD, iUPD status will be disregarded for determination of iPFS.

Table 2 iPFS Definition

iPFS		
Situation	**Date of Event or Censor**	**Outcome**
No evaluable post-baseline imaging assessments, no death	Date of first dose (Day 1)	Censor
Participant did not receive new anti-cancer therapy:		
iCPD	First date where iUPD criteria are met	Event
No iCPD, but death recorded on eCRF	Date of death	Event
No iCPD nor death and not in one of the following cases :a)if the participant stops protocol treatment because they were not judged to be clinically stable, b) no further response assessments are done (because of participant refusal, protocol non-compliance, or participant death); c) the	Date of last radiological assessment	Censor

iPFS		
Situation	**Date of Event or Censor**	**Outcome**
next timepoint responses are all iUPD, and iCPD never occurs;		
No iCPD nor death and is in one of the following cases : a)if the participant stops protocol treatment because they were not judged to be clinically stable, b) no further response assessments are done (because of participant refusal, protocol non-compliance, or participant death); c) the next timepoint responses are all iUPD, and iCPD never occurs;	First date where iUPD criteria are met	Event
Participant received new anti-cancer (ACT) therapy:		
No progression before new ACT	Date of last radiological assessment before start of new anti-cancer therapy	Censor
iCPD before new ACT	First date where iUPD criteria are met	Event
iUPD before new ACT and not in one of the following cases : a)if the participant stops protocol treatment because they were not judged to be clinically stable, b) no further response assessments are done (because of participant refusal, protocol non-compliance, or participant death); c) the next timepoint responses are all iUPD, and iCPD never occurs;	Date of last radiological assessment before start of new anti-cancer therapy	Censor
iUPD before new ACT and is in one of the following cases : a)if the participant stops protocol treatment because they were not judged to be clinically stable, b) no further response assessments are done (because of participant refusal, protocol non-compliance, or participant death); c) the next timepoint responses are all iUPD, and iCPD never occurs;	First date where iUPD criteria are met	Event
Missed >=2 scheduled radiological assessments		
If last assessment prior to missing >= 2 scans is iUPD	First date where iUPD criteria are met	Event
If last assessment prior to missing >= 2 scans is not iUPD and no progression or death after missing >=2 scans	Date of last radiological assessment	Censor

iPFS		
Situation	**Date of Event or Censor**	**Outcome**
No post-baseline tumor imaging prior to missing 2 scans and progression or death after missing >=2 scans	Date of first dose (Day 1)	Censor
No post-baseline tumor imaging prior to missing 2 scans and no progression or death after missing >=2 scans	Date of last radiological assessment	Censor
If radiographical progression or death occurs after missing 2 scheduled radiological assessments and last assessment prior to missing >= 2 scans is not iUPD	Date of last radiological assessment before missing 2 scans	Censor

iPFS = Date of Event or Censor – Date of First Dose +1

Missing 2 scheduled imaging assessments:

Missing 2 scheduled imaging assessments is defined as the gap between two imaging assessments being more than 140 days (2.5 times the scheduled imaging assessment interval (2.5 x 56 days)). Imaging assessments after first iUPD will be excluded from PFS derivation.

Note: Participant cannot be censored at “NE”. If NE is the only previous assessment, then iPFS will be censored at Day 1.

To apply the cut-off date to iPFS is to exclude those tumor assessments after cut-off date and anti-cancer therapy date after cut-off date in the analysis.

5.1.2.6 Progression-free Survival per RECIST v1.1 (PFS)

PFS is defined as the time from the start of the study treatment until death from any cause or radiographic disease progression assessed per RECIST v1.1 by investigator assessment, whichever occurs first.

Table 3 PFS Definition

PFS		
Situation	**Date of Event or Censor**	**Outcome**
No evaluable post-baseline imaging assessments, no death	Date of first dose (Day 1)	Censor
Participant did not receive new anti-cancer therapy:		
Radiographical progression documented per RECIST v1.1	Date of radiological disease progression	Event

PFS		
Situation	**Date of Event or Censor**	**Outcome**
No radiographical progression, but death recorded on eCRF	Date of death	Event
Neither radiographical progression nor death	Date of last disease assessment	Censor
Participant received new anti-cancer (ACT) therapy:		
Radiographical progression documented per RECIST v1.1 after new ACT	Date of last radiological assessment before start of new anti-cancer therapy	Censor
Radiographical progression documented per RECIST v1.1 before new ACT	Date of radiological disease progression	Event
No radiographical progression before new ACT but death recorded	Date of last radiological assessment before start of new anti-cancer therapy	Censor
No radiographical disease progression nor death	Date of last radiological assessment before start of new anti-cancer therapy	Censor
Missed >=2 scheduled radiological assessments		
If radiographical progression or death occurs after missing 2 scheduled radiological assessments	Date of last radiological assessment before missing 2 scans	Censor

PFS = Date of Event or Censor – Date of First Dose +1

Missing 2 scheduled imaging assessments:

Missing 2 scheduled imaging assessments is defined as the gap between two imaging assessments being more than 140 days (2.5 times the scheduled imaging assessment interval (2.5 x 56 days)). Imaging assessments after first iUPD will be excluded in PFS derivation.

Note: Participant cannot be censored at “NE”. If NE is the only previous assessment, then PFS will be censored at Day 1.

To apply the cut-off date to PFS is to exclude those tumor assessments after cut-off date and anti-cancer therapy date after cut-off date in the analysis.

5.1.2.7 Duration of Response per iRECIST (iDOR)

iDOR is defined as the time from the date of the first response iCR/iPR (whichever is first recorded) to the date of radiographical progression or date of censoring. iDOR will be

calculated only for the subgroup of participants with confirmed response iCR/iPR per iRECIST separately for investigator assessment.

Table 4 iDOR Definition

iDOR		
Situation	**Date of Event or Censor**	**Outcome**
Participant did not receive new anti-cancer therapy		
iCPD	First date where iUPD criteria are met	Event
No iCPD nor death and NOT in one of the following cases : a) the participant stops protocol treatment because they were not judged to be clinically stable, b) no further response assessments are done (because of participant refusal, protocol non-compliance, or participant death); c) the next timepoint responses are all iUPD, and iCPD never occurs;	Date of last radiological assessment	Censor
No iCPD nor death and is in one of the following cases : a) the participant stops protocol treatment because they were not judged to be clinically stable, b) no further response assessments are done (because of participant refusal, protocol non-compliance, or participant death); c) the next timepoint responses are all iUPD, and iCPD never occurs;	First date where iUPD criteria are met	Event
Participant received new anti-cancer therapy		
No progression before new ACT	Date of last radiological assessment before start of new ACT	Censor
iCPD before new ACT	First date where iUPD criteria are met	Event
iUPD before new ACT and NOT in one of the following cases : a) the participant stops protocol treatment because they were not judged to be clinically stable, b) no further response assessments are done (because of participant refusal, protocol non-compliance, or participant death); c) the next timepoint responses are all iUPD, and iCPD never occurs;	Date of last radiological assessment before start of new ACT	Censor

iDOR		
Situation	**Date of Event or Censor**	**Outcome**
Participant did not receive new anti-cancer therapy		
iUPD before new ACT and is in one of the following cases : a) the participant stops protocol treatment because they were not judged to be clinically stable, b) no further response assessments are done (because of participant refusal, protocol non-compliance, or participant death); c) the next timepoint responses are all iUPD, and iCPD never occurs;	First date where iUPD criteria are met	Event
Missed >=2 scheduled radiological assessments		
If last assessment prior to missing >= 2 scans is iUPD	First date where iUPD criteria are met	Event
If last assessment prior to missing >= 2 scans is not iUPD and no progression after missing >=2 scans	Date of last radiological assessment	Censor
If radiographical progression occurs after missing 2 scheduled radiological assessments and last assessment prior to missing >= 2 scans is not iUPD	Date of last radiological assessment before missing 2 scans	Censor

iDOR = Date of Event or Censor – Date of First iCR/iPR +1

Missing 2 scheduled imaging assessments:

Missing 2 scheduled imaging assessments is defined as the gap between two imaging assessments being more than 140 days (2.5 times the scheduled imaging assessment interval (2.5 x 56 days)). Imaging assessments after first iUPD will be excluded in DOR derivation.

Note: Participant cannot be censored at “NE”. If NE is the only previous assessment, then DOR/iDOR will be censored at Day 1.

To apply the cut-off date to DOR/iDOR is to exclude those tumor assessments after cut-off date and anti-cancer therapy date after cut-off date in the analysis.

5.1.2.8 Duration of Response per RECIST v1.1 (DOR)

DOR is defined as the time from the date of the first response CR/PR (whichever is first recorded) to the date of radiographical progression or date of censoring. DOR will be calculated only for the subgroup of participants with confirmed response CR/PR per RECIST v1.1, separately for investigator assessment.

Table 5 DOR Definition

DOR		
Situation	**Date of Event or Censor**	**Outcome**
Participant did not receive new anti-cancer therapy		
Radiographical progression documented per RECIST v1.1	Date of radiological PD	Event
No radiographical progression	Date of last radiological assessment	Censor
Participant received new anti-cancer therapy		
Radiographical progression documented per RECIST v1.1 after new ACT	Date of last radiological assessment before start of new anti-cancer therapy	Censor
Radiographical progression documented per RECIST v1.1 before new ACT	Date of radiological PD	Event
No radiographical progression	Date of last radiological assessment before start of new anti-cancer therapy	Censor
Missed >=2 scheduled radiological assessments		
If radiographical progression or death occurs after missing 2 scheduled radiological assessments	Date of last radiological assessment before missing 2 scans	Censor

DOR = Date of Event or Censor – Date of First CR/PR +1

Missing 2 scheduled imaging assessments:

Missing 2 scheduled imaging assessments is defined as the gap between two imaging assessments being more than 140 days (2.5 times the scheduled imaging assessment interval (2.5 x 56 days)).

5.2 Safety Endpoints

Safety and tolerability (determine MTD) are the primary endpoints of the study. Safety endpoints are adverse events (AEs), laboratory measurements, vital signs, physical examination and ECOG performance status (PS). Safety will be assessed by evaluation of the following variables:

5.2.1.1 Dose-Limiting Toxicity (DLT)

A DLT is defined as any of the listed events that occur within 28 days starting with the first dose on cycle 1 day 1 (C1D1) and that is considered to be related to IP. Confirmation of DLTs will be made by the DESC. The severity of AEs will be assessed according to the

National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE).

5.2.1.2 ASP7517 Monotherapy Arm Dose-Limiting Toxicities (DLTs)

For participants in the ASP7517 monotherapy DLT is defined in the protocol in section 4.1.

5.2.1.3 ASP7517 and Pembrolizumab Combination Therapy Arm Dose-Limiting Toxicities (DLTs)

For participants in the ASP7517 and Pembrolizumab combination therapy arm, DLT is defined in the protocol in section 4.1.

Participants who are tolerating IP at a dose level that is being reviewed due to the occurrence of DLTs in another participant will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as tolerated unless directed otherwise as a result of the safety review by the DESC.

Dose escalation within individual participants will not be allowed.

5.2.1.4 Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)

Maximum Tolerated Dose

The MTD determination will be based on at least 6 evaluable participants at that dose level based on the BOIN design. Based on the observed DLT(s) during the DLT observation period, the MTD is the highest dose for which the isotonic estimate of the DLT rate is closest to, but not over, the target DLT rate of 0.30 for monotherapy and combination therapy.

The dose level determined to be the MTD must have data from at least 6 participants.

Determination of MTD will be done for monotherapy and combination therapy separately.

Recommended Phase 2 Dose

The sponsor, in conjunction with the DESC, will determine the RP2D of ASP7517 as a single agent and in combination with pembrolizumab taking into consideration the safety and efficacy data, as well as other available data, such as pharmacokinetics and pharmacodynamics of ASP7517. The RP2D will not exceed the MTD.

The dose level determined to be the RP2D must have data from at least 6 participants.

Determination of RP2D will be done for monotherapy and combination therapy separately.

5.2.1.5 Adverse Events (AEs)

AEs will be coded using MedDRA v26.0 and graded using NCI CTCAE.

A treatment-emergent adverse event (TEAE) is defined as an AE observed after starting administration of the IP and 30 days after the final administration of IP. An IP-related TEAE is defined as any TEAE with at least possible relationship (possibly or probably related) to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

The number and percentage of participants with TEAEs, IP-related TEAEs, serious TEAEs, IP-related serious TEASs, TEAEs leading to withdrawal of treatment and IP related TEAEs leading to withdrawal of treatment will be summarized by SOC, preferred term and treatment group. The number and percentage of TEAEs by severity will also be summarized. The worst severity will be summarized if the same AE is recorded more than once for a participant. If an AE is observed with different relationships to study drug then the AE will be counted under its maximum relationship only. In case the AE relationship is not reported, it will be treated as the maximum relationship.

If the adverse event occurs on Day 1 and the onset check box is marked "Onset after first dose of study IP" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on Day 1 and the onset check box is marked "Onset before first dose of study IP", then the adverse event will not be considered treatment emergent. If a participant experiences an event both during the preinvestigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e. it is reported with a new start date). All adverse events collected that begin within 30 days after taking the last dose of study IP will also be counted as TEAE.

Immune-related AE (irAE) and infusion related reactions (IRR) will be considered as Adverse Events of Special Interest (AEsi). The list of events classified as AEsi may change during the study due to ongoing pharmacovigilance.

Time to first onset of irAE will follow the following algorithm:

Situation	Date of Event or Censor	Outcome
AE of interest observed	Date of first onset	Event
No AE of interest observed and treatment ongoing	Date of data cutoff	Censor
No AE of interest observed and treatment discontinued	Date of last dose + 30 days	Censor

Time to First Onset = Date of Event or Censor – Date of First Dose +1

5.2.1.6 Laboratory Assessments

Clinical laboratory variables for hematology, chemistry including liver function test, coagulation, urinalysis, and bone marrow will be collected during the conduct of the study as listed in Table 6 below.

Additional laboratory tests should be performed according to institutional standard of care.

Table 6 Laboratory Assessments

Clinical Laboratory Tests

Panel/Assessments	**Parameters to be Analyzed**	NCI-CTCAE Grading (Hyper/Hypo)
CBC with Differential	Hematocrit (Hct)	NA
	Hemoglobin (Hgb)	Both
	Platelet count	Hypo
	Red blood cell count (RBC)	NA
	White blood cell count (WBC)	Both
	White blood cell count differential	NA
	Absolute neutrophil count	Hypo
	Absolute lymphocyte count	Both
Biochemistry	Sodium (Na)	Both
	Potassium (K)	Both
	Chloride (Cl)	NA
	Bicarbonate (HCO3)	NA
	Blood urea nitrogen (BUN)	NA
	Creatinine (Cr)	Hyper
	Glucose (Gl)	Both
	Calcium (Ca)	Both
	Phosphorus	NA
	Magnesium (Mg)	Both
	Albumin (Alb)	Hypo
	Total protein (T Prot)	NA
	Alkaline phosphatase (ALP)	Hyper
	Lactate dehydrogenase (LDH)	NA
	Creatine phosphokinase (CPK)	Hyper
	Liver function tests including*:	
	Bilirubin total (TBL)	Hyper
	Alanine aminotransferase (ALT)	Hyper
	Aspartate aminotransferase (AST)	Hyper

Table continues next page

Panel/Assessments	**Parameters to be Analyzed**	NCI-CTCAE Grading (Hyper/Hypo)
Urinalysis	Color	NA
	Appearance	NA
	Specific gravity	NA
	pH	NA
	Bilirubin	NA
	Blood	NA
	Glucose	NA
	Ketones	NA
	Leukocyte esterase	NA
	Nitrite	NA
	Protein	NA
	Urobilinogen	NA
Urine/Serum Pregnancy Test *	hCG (Positive/Negative)	NA
Coagulation Profile (PT/INR, D-Dimer, Fibrinogen)	Activated partial thromboplastin time (aPTT)	Hyper
	International normalized ratio (INR)	Hyper
	Prothrombin time (sec) (PT)	NA
	Fibrinogen	NA
	D-Dimer	NA

eCRF: electronic case report form; hCG: human chorionic gonadotrophin.

* Local results will be collected and entered into the eCRF.

5.2.1.7 Vital Signs

Vital signs will include:

- Systolic and diastolic blood pressures (mmHg)
- Pulse rate (beats/minute)
- Respiratory Rate (breaths/min)
- Body temperature (degrees C)
- Height (m) (Height measurement performed at screening only) and weight (kg)

5.2.1.8 Electrocardiogram (ECG)

12-lead ECGs will be recorded in triplicate at the scheduled time points. Each ECG tracing will be taken 2 minutes apart. ECGs will be read at the site for clinical decision making and transmitted to a central reviewer. Data from the central reviewer will be used in summary presentations.

5.2.1.9 Eastern Cooperative Oncology Group Performance Status (ECOG PS)

The ECOG Scale [Oken et al., 1982] will be used to assess performance status at time points outlined in the Protocol in the Schedule of Assessments.

5.3 Pharmacokinetic Variables

Cellular DNA load of ASP7517and serum concentrations of Pembrolizumab will be evaluated for each cohort as outlined in the Protocol in the Schedule of Assessments.

5.4 Pharmacodynamic Variables

Pharmacodynamic effects of ASP7517 as monotherapy or in combination with pembrolizumab will be assessed with:

- Cytokine expression and secretion (e.g., IFNg)
- WT1-specific T lymphocytes (e.g., cytotoxic T lymphocytes)
- Immune cell populations (NKT cells, NK cells, etc.)
- Anti-WT1 antibodies
- Tumor microenvironment variables

5.5 Other Variables

- Duration of exposure (days)
  - Duration of exposure to a study drug will be calculated in days, using the following formula:
  - (Last date of exposure – date of first dose) + 1; where last date of exposure= initial infusion date of the last cycle + 27 or death date if death occurs within last cycle.
    - When the start or stop date is missing, then the exposure will be treated as missing.
- Cumulative actual dose (# of cells)
  - Total amount of IP administered to the participant from first dose date to last dose date
- Number of cycles initiated
  - Total number of cycles with non-zero dosing in the cycle
- Planned dose intensity
  - Planned dose/planned number of cycles
- Actual dose intensity
  - Defined as the cumulative actual dose divided by number of cycles
- Relative dose intensity (RDI; %)
  - $\frac{\text{Actual Dose Intensity}}{\text{Planned Dose Intensity}} \times 100$

6 STATISTICAL METHODOLOGY

6.1 General Considerations

For continuous variables, descriptive statistics will include the number of participants (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g.10%, 25%, 75% and 90%) will be reported in the relevant section. In addition, for plasma concentrations and continuous PK parameters, the coefficient of variation and the geometric mean will also be calculated. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of participants with no missing data, i.e. will add up to 100%. Kaplan-Meier estimates will be calculated for time-to-event variables and median survival time will be estimated with 2-sided 90% confidence intervals (CI).

Baseline is defined as the last available measurement prior to the first dose of study drug.

Unless otherwise specified, all summaries will be presented overall, by dose level received, and by phase. Separate displays will be presented for monotherapy and combination therapy cohort unless specified otherwise.

All data processing, summarization, and analyses will be performed using SAS® Version 9.4 or higher on Linux. Specifications for table, figure, and data listing formats can be found in the TLF specifications for this study.

Study day will be calculated in reference to the first dose date. For assessments conducted before the first dose, study day will be calculated as (assessment date – first dose date). For assessments conducted on or after the first dose, study day will be calculated as (assessment date – first dose date + 1).

6.2 Study Population

6.2.1 Disposition of Participants

The following participant data will be presented:

- Number and percentage of participants with informed consent, discontinued before allocation to treatment, allocated to treatment (overall only)
- Number and percentage of participants allocated to treatment in each analysis set
- Number and percentage of participants completed and discontinued treatment, by primary reason for treatment discontinuation for SAF
- Number and percentage of participants completed and discontinued the study, by primary reason for study discontinuation for SAF by dose level
- Number and percentage of participants completed and discontinued the study at 30-, 60-, and 90-day follow-up, by primary reason for post-study period discontinuation for SAF
- Number and percentage of participants completed and discontinued the study during the observation period, by primary reason for post-study period discontinuation for SAF

- Number and percentage of participants completed and discontinued the study during the survival follow-up period, by primary reason for post-study period discontinuation for SAF
- For the combination therapy arm, separate summaries for ASP7517 and Pembrolizumab will be provided for End of Treatment disposition.

All disposition details and dates of first and last evaluations for each participant will be listed.

6.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.1.6 Protocol Deviations) will be assessed for all participants enrolled. The number and percentage of participants meeting any criteria will be summarized for each criterion and overall, by dose level, phase, tumor type, and overall as well as by study site. Participants deviating from a criterion more than once will be counted once for the corresponding criterion. Any participants who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and participant.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

PD5 – Informed Consent: Clinical study procedures conducted prior to subject signing informed consent.

PD6 – Safety Reporting: Events not reported within the expected turn-around time per protocol reporting requirements.

PD7 – Procedures and Tests: Missed safety or efficacy assessments related to primary or key secondary endpoints.

6.2.3 Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics.

Number and percentage of participants allocated to treatment in each country and site will be presented by dose level, phase, tumor type, and overall for SAF and FAS.

Descriptive statistics for age, weight, and height at study entry will be presented. Frequency tabulations for sex, ethnicity, age group (>=65 years and <65 years of age), race, region, and baseline ECOG will be presented. This will be done for FAS and RAS.

Medical history and conditions existing at baseline will be coded in MedDRA v26.0 and summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by treatment group and overall for the SAF. Baseline conditions are defined as those ongoing

at the time of informed consent or arise following the time of informed consent and before the first dose of study drug. For ongoing medical conditions, Common Terminology Criteria for Adverse Events (CTCAE) grade will be provided in listing.

6.2.4 Disease History

Frequency tabulations will be presented for disease history including tumor subtype and prior anti-cancer therapies.

6.2.5 Previous and Concomitant Medications

Previous medications include medications taken within 28 days prior to cycle 1 day 1 and all anticancer treatment received 28 days prior to IP administration. Previous medications are coded with WHO-DD, and will be summarized in descending percentage order by Preferred WHO Name (Ingredients), as well as by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by dose level, phase, tumor type, and overall for the SAF.

Concomitant medications include medications taken after the first dose of study drug up until the 90 days follow-up visit. As with previous medication, concomitant medication will be summarized by dose level, phase, tumor type, and overall, in descending percentage order by Preferred WHO Name (Ingredients), as well as by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Participants taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

6.2.6 Prior Radiation Therapy

Frequency tabulations of participants with prior radiation therapy will be presented for SAF.

6.2.7 Non-Medication Therapy

Frequency tabulations of participants with non-medication therapy and reason for use will be presented by dose level, phase, tumor type, and overall for SAF. Number of non-medication therapy received per participant will be summarized using descriptive statistics.

6.2.8 Prior and New Anti-Cancer Therapy

Frequency tabulations of participants with prior or new anti-cancer therapy will be presented for SAF.

6.3 Study Drug

6.3.1 Exposure

The following information on drug exposure will be presented with descriptive statistics (n, mean, standard deviation, median, minimum, maximum) for the SAF:

- Duration of exposure (days)
- Cumulative actual dose (# of cells)
- Number of cycles initiated

- Planned dose intensity
- Actual dose intensity
- Relative dose intensity (RDI; %); in addition to descriptive statistics, frequency tabulations will be presented for RDI for the following categories:
  - <50%
  - 50% to <=80%
  - >80%
  - Unknown

Number and percentage of participants with dose adjustments, or interruptions and reasons for dose adjustments and interruptions will be presented for the SAF.

6.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and RAS (RAS for response-related analyses, FAS for overall survival and other time-to-event analyses). Tumor related analyses are summarized based on RECIST 1.1 and iRECIST. Efficacy analyses will be summarized by dose level, phase, and tumor type. Swimmer plots will be produced displaying participants' overall disease response experience, and waterfall plots to display maximum tumor shrinkage rate.

6.4.1 Analysis of Primary Efficacy Endpoint

6.4.1.1 Objective Response Rate per iRECIST (iORR)

iORR with confirmed response by investigator assessment will be calculated for each group and its 95% confidence interval will be constructed by Clopper-Pearson method. To assess sensitivity, iORR will also be estimated and its 95% confidence interval will be constructed by Clopper-Pearson method for the endpoints:

- iORR with confirmed response by investigator assessment
- iORR with unconfirmed response by investigator assessment

6.4.2 Analysis of Secondary Efficacy Endpoints

6.4.2.1 Objective Response Rate per RECIST v1.1(ORR)

ORR for each group will be calculated and its 95% confidence interval will be constructed by Clopper-Pearson method for the endpoints of:

- ORR with confirmed response by investigator assessment
- ORR with unconfirmed response by investigator assessment

6.4.2.2 Disease Control Rate per iRECIST (iDCR)

iDCR for each group will be calculated and its 95% confidence interval will be constructed by Clopper-Pearson method by investigator assessment for the endpoints of:

- iDCR with confirmed response by investigator assessment
- iDCR with unconfirmed response by investigator assessment

6.4.2.3 Disease Control Rate per RECIST v1.1 (DCR)

DCR for each group will be calculated and its 95% confidence interval will be constructed by Clopper-Pearson method by investigator assessment for the endpoints of:

- DCR with confirmed response by investigator assessment
- DCR with unconfirmed response by investigator assessment

6.4.2.4 Overall Survival (OS)

OS will be estimated and summarized for each dose level and treatment group using Kaplan-Meier methodology for investigator assessments of radiological scans. OS will be also listed.

6.4.2.5 Progression-Free Survival per iRECIST (iPFS)

iPFS will be estimated and summerized for each group using Kaplan-Meier methodology for investigator assessments of radiological scans. iPFS will be listed.

6.4.2.6 Progression-Free Survival per RECIST v1.1 (PFS)

PFS will be estimated and summarized for each group using Kaplan-Meier methodology for investigator assessments of radiological scans. PFS will be listed.

6.4.2.7 Duration of Response per iRECIST (iDOR)

iDOR will be listed.

6.4.2.8 Duration of Response per RECIST v1.1 (DOR)

DOR will be listed .

6.5 Analysis of Safety

Safety analyses will be conducted using the SAF. Safety analyses will be summarized by dose level, phase, tumor type, and overall.

6.5.1 Dose Limiting Toxicities

Dose evaluation and dose escalation stopping rules based on the BOIN design with target DLT rate of 0.30 and optimal interval of (0.236, 0.359) are as follows:

Action	Number of Participants Treated at Current Dose Level					
	3	**4**	**5**	**6**	**7**	**8**
Escalate dose if number of participants with DLT ≤	0	0	1	1	1	1
Stay at current dose level if number of participants with DLT =	1	1	-	2	2	2
De-escalate if number of participants with DLT =	2	2	2 or 3	3	3 or 4	3 or 4
Stop if number of participants with DLT ≥	3	3	4	4	5	5

DLT: dose limiting toxicity

6.5.2 Adverse Events

For the purpose of safety assessments in this study, events recorded during the pre-investigational period will be classified as Baseline Signs and Symptoms. All adverse events (AE) recorded on treatment including within 30 days from the last study treatment and serious adverse events (SAEs) on treatment including within 90 days of the last study treatment will be summarized.

Summaries and listings of SAEs and Serious TEAEs include SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms if any upgrade was done.

The coding dictionary for this study will be MedDRA v26.0. It will be used to summarize AEs by SOC and PT. AEs will be graded using National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE).

An overview table will include the following details by dose level, phase, tumor type, and overall:

- Number and percentage of participants with TEAEs
- Number and percentage of participants with IP related TEAEs
- Number and percentage of participants with TEAE leading to death
- Number and percentage of participants with IP-related TEAE leading to death
- Number and percentage of participants with serious TEAEs and Astellas upgraded serious TEAE
- Number and percentage of participants with serious IP related TEAEs and Astellas upgraded serious IP related TEAE
- Number and percentage of participants with TEAEs leading to permanent discontinuation of study IP
- Number and percentage of participants with IP related TEAEs leading to permanent discontinuation of study IP
- Number and percentage of participants with CTCAE grade 3 or higher TEAE
- Number and percentage of participants with CTCAE grade 3 or higher IP related TEAE

The number and percentage of participants with TEAEs, as classified by SOC and PT will be summarized by dose level, phase, tumor type, and overall. Summaries will be provided for:

- DLTs within the DLT observation period
- TEAEs
- Deaths
- IP related TEAEs
- Serious TEAEs and Astellas upgraded serious TEAE
- IP related serious TEAEs and IP related Astellas upgraded serious TEAE
- TEAEs leading to permanent discontinuation of study IP
- IP related TEAEs leading to permanent discontinuation of study IP
- CTCAE Grade 3 or higher TEAEs
- IP-related CTCAE Grade 3 or higher TEAEs
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5% in any dose level
- common TEAEs that equal to or exceed a threshold of 5% in any dose level
- Late SAEs occurring beyond 30 days from last study treatment

The number and percentage of participants with TEAEs, and TEAEs leading to death, as classified by PT only, will be summarized by dose level, phase, tumor type, and overall.

AE summary tables will include participant counts as opposed to AE counts. If a participant experiences more than one episode of a particular AE, that participant will be counted only once for that event. If a participant has more than one AE that code to the same preferred term, the participant will be counted only once for that preferred term. Similarly, if a participant has more than one AE within a body system, the participant will be counted only once in that body system.

The number and percentage of participants with TEAEs, as classified by SOC and PT will also be summarized by NCI-CTCAE severity grade, and by relationship to study drug. In the participant count, if a participant has multiple TEAEs with the same SOC or PT, but with differing severity grade or relationship, then the participant will be counted only once with the worst severity grade and highest degree of relationship, however, if any of the severity grade or relationship values are missing then the participant will be counted only once with missing severity grade or relationship.

The number and percentage of participants with TEAEs, as classified by SOC and PT will be summarized by dose level for SAF.

All AEs, deaths, SAEs, withdrawals due to adverse events, and AEs for re-screened participants will be displayed in listings.

The list of adverse events to be summarized may change during the course of the study due to ongoing pharmacovigilance.

6.5.3 Adverse Events of Special Interest (AEsi)

The number and percentage of participants with Adverse Events of Special Interest (AEsi) such as IRR, irAE, and as classified by SOC and PT, will be summarized by dose level, phase, tumor type, and overall.

6.5.4 Clinical Laboratory Evaluation

The baseline visit is the last measurement taken prior to initial study IP administration.

Frequency tabulations of qualitative clinical laboratory variables will be presented at each visit.

Laboratory results will also be graded using NCI-CTCAE, where possible. Following the Table 6 in section 5.2.1.6, parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same participant can be counted for both values if the participant has different laboratory values meeting each criterion. NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of participants for each visit. Shift tables of NCI-CTCAE grade change from baseline to worst post-baseline grade will also be presented. The number and percentage of participants with grade 3 or 4 laboratory test results will be summarized by dose level, phase, tumor type, and overall, and laboratory parameter (the name of the adverse event associated with the abnormal laboratory test result) will be presented.

Laboratory results will be listed.

6.5.4.1 Liver Safety Assessment

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The participant's highest value during the investigational period will be used.

Parameter	Criteria
ALT	> 3xULN > 5xULN > 10xULN > 20xULN
AST	> 3xULN > 5xULN > 10xULN > 20xULN
ALT or AST	> 3xULN > 5xULN > 10xULN > 20xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin(*)	(ALT and/or AST > 3xULN) and (Total bilirubin > 2xULN)
ALT and/or AST AND Total Bilirubin AND ALP (*)	(ALT and/or AST > 3xULN) and Total bilirubin > 2xULN and ALP < 2xULN

(*) Combination of values measured within same sample

The number and percentage of participants with potentially clinically significant values in liver enzymes and total bilirubin during the investigational period will be presented by dose level, phase, tumor type, and overall.

6.5.5 Vital Signs

The baseline value is the last measurement taken prior to the first study drug administration.

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, respiratory rate, body temperature and weight) will be summarized using mean, standard deviation, minimum, maximum and median by dose level, phase, tumor type, and overall. Additionally, a within-participant change will be calculated per visit as the post-baseline measurement minus the baseline measurement and summarized by visit. Within-participant change will also be calculated from pre-dose and reported.

Tables for potentially clinically significant vital signs will be generated using baseline value and highest post-baseline value for each participant.

The following criteria are defined as clinically significant for each parameter:

Vital Sign Variable	**Criteria**
SBP	≥180 mmHg AND ≥20 mmHg change from baseline
DBP	≥105 mmHg AND ≥15 mmHg change from baseline
Pulse Rate	≥120 bpm AND ≥15 bpm change from baseline

Vital signs data will be displayed in listings.

6.5.6 Electrocardiograms (ECGs)

The three values of each ECG parameter within a time point from the central reviewer will be averaged to determine time-specific parameter for a participant, and used in summaries.

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median for each dose level, phase, tumor type, and overall at each treatment visit and time point, including changes from baseline.

Number and percentage of participants with normal and abnormal results as assessed by central review for the overall interpretation will be tabulated by dose level, phase, tumor type, and overall at each treatment visit and time point. A shift analysis table showing shift in overall ECG interpretation from baseline to each time point will be provided. The worst of the three overall ECG interpretations will be used as the time-specific overall ECG interpretation for a participant.

The QT interval corrected for heart rate by Fridericia's formula, QTcF, is defined as: $QTc\ (F) = QT/(RR)^{0.33}$, where RR interval is inversely proportional to heart rate (approximately RR = 60/heart rate).

The QTcF interval will be summarized using frequency tables for each treatment visit and time point for values of clinical importance using the range criteria below.

	QTc Interval Criteria Value (msec)	
	Cumulative Category	**Interval Category**
Normal	≤ 450	≤ 450
Borderline	> 450	> 450 to ≤ 480
Prolonged	> 480	> 480 to ≤ 500
Clinically significant	> 500	> 500

The QTcF interval will also be summarized by the frequencies of participants with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided for each treatment visit and time point.

	Change from Baseline	
Variable	**Cumulative Category**	**Interval Category**
QTc Interval (msec)	<0 ≥ 0 > 30 > 60	<0 ≥ 0 to ≤ 30 > 30 to ≤ 60 > 60

Number and percent of participants with 12 lead ECG abnormalities as well as number and percent of participants whose 12 lead ECG reading changed from normal at baseline to abnormal will be tabulated by dose level, phase, tumor type, and overall at each treatment visit and time point.

6.5.7 Pregnancies

A detailed listing of all pregnancies will be provided.

6.5.8 Eastern Cooperative Oncology Group (ECOG) Performance Status

Number and percent of participants for each category of the ECOG performance status at each assessment time will be provided. The change from baseline to EOT score will also be summarized. Negative change scores indicate an improvement. Positive change scores indicate a decline in performance.

ECOG will also be summarized using shift table from baseline to post-baseline score for each dose level, phase, tumor type, and overall by visit.

6.6 Analysis of Pharmacokinetics

Cellular DNA load and kinetic parameters of ASP7517, as well as serum concentration of pembrolizumab will be summarized by using descriptive statistics including n, mean, standard deviation, minimum, median, maximum, coefficient of variation (CV), geometric mean, and geometric CV. Spaghetti and mean time-course of cellular DNA load will be constructed.

6.6.1 Estimation of Pharmacokinetic Parameters

Participants with sufficient cellular DNA samples will have kinetic parameter estimates for ASP7517 including calculation of AUC, C_{max}, and t_{max}. for each cycle estimated by the pharmacokineticist using a non-compartmental analysis method in reference to Manual for Non-Compartmental Analysis of Pharmacokinetic Data from Studies using PhoenixTM® WinNonlin® (Certara, Saint Louis, Missouri, US) software version 6.4 or higher.

Exploratory analysis between pharmacokinetic parameters and clinical measures (e.g., efficacy or safety) may be performed.

6.7 Analysis of Exploratory Endpoints

Biomarkers/Pharmacodynamics

Immune cell phenotyping biomarkers will be summarized by change from baseline at each time point by both absolute number and percentage.

6.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

No interim analysis to be performed.

6.9 Additional Conventions

6.9.1 Analysis Windows

No visit window will be used; nominal visit date will be considered date of visit.

6.9.2 Imputation Rules for Incomplete Dates

Missing or partial start and stop dates of adverse events, concomitant medications, and new anti-cancer therapy will be imputed according to Astellas standards using the following algorithm:

- Imputation rules for partial or missing stop dates:
  - If the month and year are present, then impute as the last day of that month.
  - If only the year is present, impute as December 31 of that year.
  - If the stop date is entirely missing, assume the event or medication is ongoing.
- Imputation rules for partial or missing start dates:

Start Date		Stop Date: Complete: *yyyymmdd*		Stop Date: Partial: *yyyymm*		Stop Date: Partial: *yyyy*		Stop Date: missing
		< 1st dose	**≥ 1st dose**	**< 1st dose *yyyymm***	**≥ 1st dose *yyyymm***	**< 1st dose *yyyy***	**≥ 1st dose *yyyy***	
Partial: *yyyymm*	= 1st dose *yyyymm*	2	1	2	1	n/a	1	1
	≠ 1st dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	= 1st dose *yyyy*	3	1	3	1	n/a	1	1
	≠ 1st dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute as the date of first dose; 2 = Impute as the first of the month; 3 = Impute as January 1 of the year; 4 = Impute as January 1 of the stop year

For survival and other time-to-event endpoints, missing or incomplete death date will be imputed as the earliest feasible date on or after the date last known to be alive as the examples shown in the table below.

Incomplete date of death or new anti-cancer therapy	Date Last Known to be Alive/Not Started New Treatment	Imputed Date
?? APR 2020	31 MAR 2020	01 APR 2020
14 ??? 2020	31 MAR 2020	14 APR 2020
?? ??? 2020	31 MAR 2020	31 MAR 2020
?? APR ????	31 MAR 2020	01 APR 2020
14 APR ????	31 MAR 2020	14 APR 2020
?? ??? ????	31 MAR 2020	31 MAR 2020

6.9.3 COVID-19 Impact Assessment

Assessments affected by the COVID-19 pandemic will be listed for visit-based assessments and for non-visit-based assessments.

For visit-based assessments affected by the COVID-19 pandemic, the listing shows if an assessment was not performed due to the COVID-19 pandemic, if it was out of window, if the assessment was performed at an alternative location or if it was a virtual assessment. Other information and comments reported on assessments affected by the COVID-19 pandemic are also included.

For non-visit-based assessments affected by the COVID-19 pandemic, participants who experience any of the following items: treatment discontinuation due to COVID-19, COVID-19 medical history, COVID-19 adverse event, hospitalization due to COVID-19, dose changing due to COVID-19, or COVID-19 death, will be listed.

Any events including discontinuation of treatment, medical history, adverse events, hospitalization, dose changing, or death, which are related to COVID-19, will be identified in the corresponding listing.

6.9.4 Outliers

All values will be included in the analyses.

7 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0		Original Document	
2.0	15-SEP-2023	Endpoints by Independent Central Review have been removed in sections 5.1 Efficacy Endpoints and 6.4 Analysis of Efficacy. In Section 6.4.2 Analysis of Primary Efficacy Endpoints, OS, iPFS, PFS will be summarized and listed; iDOR, and DOR will be listed only. Select analyses have been removed from Section 6.7 Analysis of Exploratory Endpoints. Section 6.8 Subgroups of Interested has been removed. Time to first AE analyses were removed. Signature page Appendix 1: Key Contributors and Approvers Appendix 2: Author and Approver Signatures	Independent Central Review data is no longer being collected. Early termination of study and number of analyses has been reduced. Subgroup analyses no longer being performed. Analyses of time to first irAE's with Kaplan-Meier method and summary no longer being performed.

8 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

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9 APPENDICES

9.1 Appendix 1: Key Contributors and Approvers

PPD	PPD
PPD	Data Science
PPD	Medical Science
PPD	Data Science
PPD	CPED
PPD	CPED
PPD	Data Science
PPD	Regulatory Affairs
PPD	Data Science

9.2 Appendix 2 Author and Approver Signatures

Prepared by: PPD

Approved by: *E-signatures are attached at end of document* Date: _____

PPD

Date (DD MMM YYYY)

Approved by: *E-signatures are attached at end of document* Date: _____

PPD

Date (DD MMM YYYY)