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

ISN/Protocol 7517-CL-1101

Version 7.0

Incorporating Substantial Amendment 6

10 Feb 2022

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IND Grantor: CBER

Sponsor:

Astellas Pharma Global Development Inc.
1 Astellas Way
Northbrook, IL 60062, US

Protocol History:

Version 1.0 [01 Sep 2020]
Version 2.0 [04 Dec 2020] Incorporating Substantial Amendment 1
Version 3.0 [02 Mar 2021] Incorporating Substantial Amendment 2
Version 4.0 [11 May 2021] Incorporating Nonsubstantial Amendment 3
Version 5.0 [23 Jun 2021] Incorporating Substantial Amendment 4
Version 6.0 [28 Oct 2021] Incorporating Nonsubstantial Amendment 5

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SIGNATURES

AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This study will be conducted in adherence to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable laws and regulatory requirements, as well as this protocol.

This study will be conducted in compliance with Japanese regenerative medicine GCP (for Japan only). As the evidence of the agreement, the investigator (CHIKEN SEKININ ISHI) and responsible person of the sponsor (CHIKEN IRAI SEKININSHA) inscribe in the bipartite agreement by signature or "printed name and seal."

1. SPONSOR'S SIGNATURES

Required signatures (e.g., protocol authors and contributors, etc.) are located in [Section 13 Sponsor's Signatures].

2. INVESTIGATOR'S SIGNATURE

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 have read all pages of this protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my personnel have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

Date (DD-MMM-YYYY)

Printed Name: .....

<Insert name and qualification of the investigator>

Address of trial site: .....

.....

CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

24-hour Contact for Serious Adverse Events See [Section 10.3.6 Reporting Procedures for Serious Adverse Events]	**Please fax or email the serious adverse events/special situations worksheet to:** Astellas Pharma Global Development Inc. Global/US Pharmacovigilance **North America fax number: +1-888-396-3750** **North America alternate fax number: +1-847-317-1241** **Email: safety-us@astellas.com** ***Specific to Japan:*** JUTOKUNA YUUGAIJISHOU OYOBIFUGUAI HOUKOKUSHO or JUTOKUNA YUUGAIJISHOU HOUKOKUSHO and the special situations worksheet to: **Astellas Pharma Inc. - Japan** **Pharmacovigilance** **Fax number: 03-3243-5747** **Email: rk-safety-jp@jp.astellas.com**
Medical Monitor/Study Physician	PPD Astellas Pharma Global Development Inc. PPD

1 PROTOCOL SUMMARY

1.1 Synopsis

Title of Study:
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

Planned Study Period/Duration:
From approximately 2Q2021 to 4Q2024

Planned Total Number of Study Sites and Location(s):
Approximately 30 sites in Japan and US

Study Objectives and Endpoints:

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
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)

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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., IFNγ) 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; IFNγ: 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.

Study Population:

Participants with locally progressive (unresectable) or metastatic solid tumor malignancies known to express Wilms' tumor protein 1 (WT1) antigen (including but not limited to melanoma, ovarian cancer and colorectal cancer [CRC] who have received all standard therapies except checkpoint inhibitor [CPI]-naïve melanoma in phase 2).

Number of Participants:

Approximately 385 participants may be enrolled.

Phase 1 (Dose Escalation Cohort): Approximately 24 participants may be enrolled in the escalation cohorts (approximately 12 participants for monotherapy and 12 participants for combination therapy).

Phase 2 (Dose Expansion Cohort): The total number of participants in the expansion cohorts will depend on the observed antitumor activity. It is estimated that approximately 361 participants may be enrolled in the monotherapy and combination therapy arms (approximately 129 participants for monotherapy and 232 participants for combination therapy).

Study Design Overview:

This study is a phase 1/2, open-label study of ASP7517 as monotherapy and in combination with pembrolizumab in selected participants 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). Phase 2 monotherapy and combination dose expansion cohorts will be opened after the phase 1 dose escalation has been completed for the monotherapy and the combination therapy, independently.

In this study, 28 days will define each cycle during Cycles 1 to 6.
Additional cohort may be added by a protocol amendment to further evaluate ASP7517 as a single agent and/or in combination with another anti-cancer agent.

ASP7517 Monotherapy Arm

This arm will consist of Screening (up to 28 days); Treatment (up to 6 doses); End of Treatment (EOT) visit; Safety follow-up (30, 60 and 90 days); Observation Period (up to 48 weeks); and Survival follow-up (up to 12 months).
Participants will receive 1 dose of ASP7517 on Day 1 of each 28-day cycle for up to 6 doses. Following the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as radiological response or stable disease [SD], or reduction of disease-related symptoms) will continue further treatment with ASP7517, as decided by the investigator.
After completing 4 cycles of treatment, participants who achieve confirmed complete response (CR) will not continue with ASP7517, and participants who achieve partial response (PR) or SD may receive an additional 2 doses. An EOT visit will be conducted for all participants within 7 days of EOT determination or prior to the initiation of new anticancer therapy, whichever occurs first. After the EOT visit, participants will complete 30-day, 60-day and 90-day safety follow-up visits.
All participants will enter an observation period except those with confirmed disease progression by immune response evaluation criteria in solid tumors (iRECIST) (iCPD), unconfirmed disease progression disease based on iRECIST (iUPD) (per independent central review or local review) and who are not clinically stable or clinical progression is confirmed by the investigator. Participants in the Observation Period will be followed for up to 48 weeks until iCPD per independent central review, initiation of a new anticancer therapy or meeting one of the Observation Period discontinuation criteria, whichever occurs first.
All participants will be followed for the survival period. Survival follow-up will be assessed by telephone calls every 3 months for up to 12 months.

ASP7517 and Pembrolizumab Combination Therapy Arm

This arm will consist of Screening (up to 28 days); Treatment period (up to 6 doses of ASP7517 in combination with up to 4 doses of pembrolizumab); Observation Period (up to 96 weeks); EOT visit; 30-day, 60-day and 90-day Safety follow-up; and Survival follow-up (up to 12 months). Pembrolizumab monotherapy may be extended up to a total of 17 doses for qualifying participants. In the combination treatment arm, ASP7517 will be given on Day 1 of each 28-day cycle for up to 6 doses in combination with pembrolizumab for up to 4 doses administered every 6 weeks, starting from Day 1 of Cycle 1. Following the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as radiological response or SD, or reduction of disease-related symptoms) will continue further treatment with ASP7517 and pembrolizumab as decided by the investigator.
Participants who achieve confirmed CR within the first 4 cycles will not receive further treatment with ASP7517 at Cycle 5 and Cycle 6 (end of Treatment period) and participants who achieve PR or SD after 4 doses may receive additional 2 doses of ASP7517 in combination with pembrolizumab.

Participants completing the Treatment period who enter the Observation Period with CR, PR or SD are allowed to continue on pembrolizumab alone up to a total of 17 doses for those participants who, in the opinion of the investigator, are continuing to derive clinical benefit.

Subsequent to the Treatment period, all participants, except those with iCPD, iUPD who are not clinically stable or have clinical disease progression per independent central review or local review, will enter the Observation Period to monitor treatment response. Participants in the Observation Period will be followed for up to 96 weeks until iCPD (confirmed by independent central review or local review), initiation of a new anticancer therapy or meeting 1 of the Observation Period discontinuation criteria, whichever occurs first. After discontinuation of investigational product (IP), all participants will complete an EOT visit, along with 30-, 60- and 90-day safety follow-up visits from the last dose of IP or prior to the initiation of new anticancer treatment.

All participants will be followed for survival, subsequent anticancer treatments and treatment outcomes following the conclusion of the Observation Period. Survival follow-up will be assessed by telephone calls every 3 months for up to 12 months.

Phase 1 Dose Escalation

Both the monotherapy and combination arms will evaluate escalating doses of ASP7517 in approximately 9 to 12 participants evaluable for dose limiting toxicities (DLTs). In the combination therapy arm, a fixed dose of 400 mg pembrolizumab will be evaluated in combination with ASP7517. The starting dose level of ASP7517 is 1 x 10^7 cells/dose. The dose of ASP7517 may be escalated to 1 x 10^8 cells/dose or de-escalated to 1 x 10^6 cells/dose based on the assessment of safety variables, including the occurrence of DLTs.

Dose escalation will be guided according the Bayesian optimal interval (BOIN) design [Liu & Yuan, 2015] to determine the next dose level based on DLT occurrence.

Study enrollment and study treatment will be temporarily interrupted during dose escalation of monotherapy or combination therapy arms pending review of the following:

- Any death that is not related to disease progression occurring within 30 days of receiving IP
- Occurrence of 2 grade ≥ 4 DLTs in 2 study participants
- Any grade 4 hypersensitivity reaction/anaphylaxis

In the Monotherapy Arm Dose Escalation Cohort, the starting dose level is 1×10^7 cells/dose and the decision to escalate to the next dose levels (1×10^8 cells/dose) will be made based on the assessment of safety variables, including the occurrence of DLTs. Dose level may be de-escalated to a lower dose level (1×10^6 cells/dose) based on the occurrence of DLTs.

The initial dose escalation cohort of ASP7517 in combination with pembrolizumab will use a dose of ASP7517 1×10^7 cells/dose. In the combination treatment arm, a 400 mg pembrolizumab infusion will be administered first, followed by an ASP7517 infusion at least 1 hour after the completion of the pembrolizumab infusion.

The decision to escalate to the next dose level (1×10^8 cells/dose) will be made based on the assessment of safety variables, including the occurrence of DLTs. A dose level of ASP7517 may be de-escalated to a lower dose level (1×10^6 cells/dose) based on the occurrence of DLTs.

Dose Escalation and Safety Committee:

A Dose Escalation and Safety Committee (DESC) consisting of sponsor representatives and investigators will convene once a dose level cohort completes the DLT observation period and data are available for review. Additional details regarding responsibilities, membership requirements and safety review time points are included in the DESC Charter. The DESC will also review the aggregate safety data from the phase 1 dose escalation and phase 2 expansion cohorts.

While safety data from the DLT observation period in the escalation cohorts are the minimum safety data needed for the DESC meeting, all available safety findings will be considered by the DESC. The DESC will assess whether a longer DLT observation period is warranted based on emerging data. Additionally, only when determining the RP2D, the DESC may choose a more conservative dosing decision than the maximum tolerated dose (MTD) selected by BOIN design, based on evaluation of the safety data and other available data.

The decision on the dose level for the next cohort will be based on the BOIN design. In addition, MTD will be determined by BOIN from at least 6 participants. The dose for phase 2 expansion will not be higher than the MTD.

Participant Replacement during Dose Escalation Cohort

Participants may be replaced in the dose escalation cohort if:

- 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 decision regarding replacement of individual participants will be made by the sponsor with discussions with the treating investigator. Participants who experience DLTs in the dose escalation cohort will not be replaced.

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:

	Number of Participants Treated at Current Dose Level					
Action	**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

Dose escalation within individual participants will not be allowed.

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.

Phase 2 Monotherapy Arm Dose Expansion Cohort

Monotherapy dose expansion will be opened after the phase 1 monotherapy arm dose escalation has been completed and RP2D is established. If confirmed response (PR based on iRECIST [iPR] or a CR based on iRECIST [iCR] per independent central review) is observed in a monotherapy arm dose escalation cohort, a tumor-specific dose expansion cohort may be opened in that tumor type after the phase 1 dose escalation has been completed. Additionally, once RP2D is determined, melanoma expansion cohort may be opened (even if no response is observed in the 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. 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]. In case the enrollment for both the monotherapy arm escalation cohort and combination arm escalation cohort therapies opens together, participants will be randomized to either monotherapy or combination cohort in 1:1 ratio.

When escalation and expansion cohorts are both open for enrollment, enrollment into escalation cohorts takes priority such that participants who are eligible for both will be preferentially enrolled in the escalation cohorts. Additionally, enrollment in the expansion cohorts may be prematurely closed at the discretion of the sponsor.

UNIQUE to Japan Sites

Japanese participants will be enrolled in the monotherapy arm of the dose expansion cohort.

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 and MTD/RP2D of ASP7517 combination therapy has been determined. Metastatic melanoma CPI naïve cohort will be opened. If 5 confirmed responses (iPR or iCR, per independent central review) were 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) was 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.

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.

UNIQUE to Japan Sites

Japanese participants will be enrolled in the monotherapy arm of the dose expansion cohort.

DLT Criteria

A DLT is defined as any of the following 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 adverse events (AEs) will be assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0.

DLTs Requiring Discontinuation of Treatment

- If a study participant develops a grade 4 DLT after receiving Cycle 1, then the study participant should not receive Cycle 2 of the study product.
- If a study participant develops a grade ≥ 3 non-hematological AE that does not resolve to ≤ grade 2 within 72 hours of onset, it should be considered a DLT and the study participant should not receive Cycle 2 of the study product.
- If there is a delay in administration of Cycle 2 by > 4 weeks, it may result in discontinuation of treatment after discussion with the sponsor.

ASP7517 Monotherapy Arm DLTs:

- Non-hematologic AEs that are ≥ grade 3 and that do not resolve to ≤ grade 2 within 72 hours of onset
- Confirmed Hy's law case
- Infusion-related reaction (IRR) that requires the infusion to be discontinued
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1
- Grade ≥ 3 thrombocytopenia accompanied by bleeding that requires transfusion or hospitalization
- Grade ≥ 3 anemia requiring transfusion
- Grade 3 febrile neutropenia with or without infection
- Grade 5 treatment-related toxicity

The following AEs will not be considered as DLTs in the ASP7517 monotherapy arm:

- Electrolyte abnormalities that are not associated with clinical sequelae or deemed not clinically significant and corrected with appropriate management or supplementation within 72 hours of onset
- Grade 3 infusion site reaction if successfully managed and resolved within 72 hours
- Alopecia, anorexia or fatigue
- Grade 3 nausea and/or vomiting if not requiring tube feeding or total parenteral nutrition, or diarrhea and/or constipation if not requiring or prolonging hospitalization that can be managed to grade ≤ 2 with standard antiemetic or antidiarrheal medications used at prescribed dose within 72 hours of onset
- Grade 3 liver function test (LFT) elevations that resolve to ≤ grade 1 within 7 days; LFT elevations lasting > 7 days that are considered to be clinically significant and at least possibly related to ASP7517 will be considered to be a DLT
- Grade 3 immune-related AEs (irAEs) that resolve to ≤ grade 1 within 72 hours of onset

ASP7517 and Pembrolizumab Combination Therapy Arm DLT:

- Grade ≥ 3 non-hematological AE that does not resolve to ≤ grade 2 within 72 hours of onset
- Grade ≥ 3 febrile neutropenia
  - Grade 3 febrile neutropenia is defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour.
  - Grade 4 febrile neutropenia is defined as ANC < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Grade ≥ 3 thrombocytopenia accompanied by bleeding that requires transfusion or hospitalization
- Grade ≥ 3 anemia requiring transfusion
- Grade ≥ 2 pneumonitis
- Grade ≥ 2 encephalopathy, meningitis, or motor or sensory neuropathy
- Confirmed Hy's law cases
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN) in participants without liver metastases
- AST or ALT > 8 × ULN in participants with liver metastases
- Total bilirubin > 3 × ULN (grade ≥ 3)
- Guillain-Barré syndrome or myasthenic syndrome/myasthenia gravis
- IRR that requires the infusion to be discontinued
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1
- Grade 5 treatment-related toxicity

Participants experiencing a DLT will be discontinued from the study unless the participants are deriving clinical benefit from the study treatment in the opinion of the investigator; in those cases, after discussion with the sponsor, participants may be allowed to continue study treatment with ASP7517 upon resolution of the DLT event to ≤ grade 1 or baseline. 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.

DLTs Requiring Discontinuation of Treatment

- If a study participant develops a grade 4 DLT after receiving Cycle 1, then the study participant should not receive Cycle 2 of the study product.
- If a study participant develops a grade ≥ 3 non-hematological AE that does not resolve to ≤ grade 2 within 72 hours of onset, it should be considered a DLT and the study participant should not receive Cycle 2 of the study product.
- If there is a delay in administration of Cycle 2 by > 4 weeks, it may result in discontinuation of treatment after discussion with the sponsor.

Treatment Groups and Duration:

Monotherapy:

Arm/IP Name	ASP7517
Use	Test product
Dose	1×10^7 cells/dose, 1×10^8 cells/dose
Frequency	Single dose on Day1 every 4 weeks
Route	Intravenous
Duration	up to 6 doses

Combination Therapy:

Arm/IP Name	ASP7517 and pembrolizumab
Use	Test product
Dose	1×10^7 cells/dose, 1×10^8 cells/dose (ASP7517); 400 mg (pembrolizumab)
Frequency	ASP7517, Single dose on Day 1 every 4 weeks Pembrolizumab, Single dose every 6 weeks
Route	Intravenous
Duration	Up to 6 doses of ASP7517 in combination with pembrolizumab; with up to 4 doses (pembrolizumab) during the treatment period; a total of 17 doses of pembrolizumab for qualifying participants

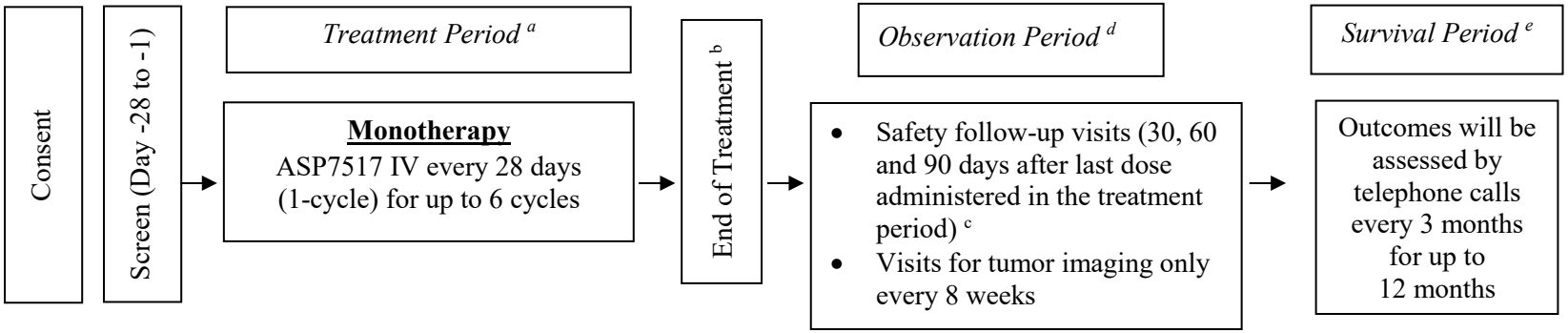
Monotherapy arm participants will receive up to 6 doses of ASP7517. The length of each cycle is 28 days. ASP7517 will be diluted with normal saline to 50 mL and administered by intravenous infusion at 4 to 6 mL/min infusion rate through a dedicated intravenous line.

Pembrolizumab will be administered as an intravenous infusion over 30 min followed by ASP7517 administration, at least 1 hour after pembrolizumab infusion through a dedicated intravenous line.

The anticipated duration of the study for each participant, including Screening and the Observation Period, is up to approximately 3 years.

1.2 Study Schema

Figure 1 Monotherapy: ASP7517



EOT: end of treatment; iCPD: "immune" confirmed progressive disease; IV: intravenous iUPD: "immune" unconfirmed progressive disease

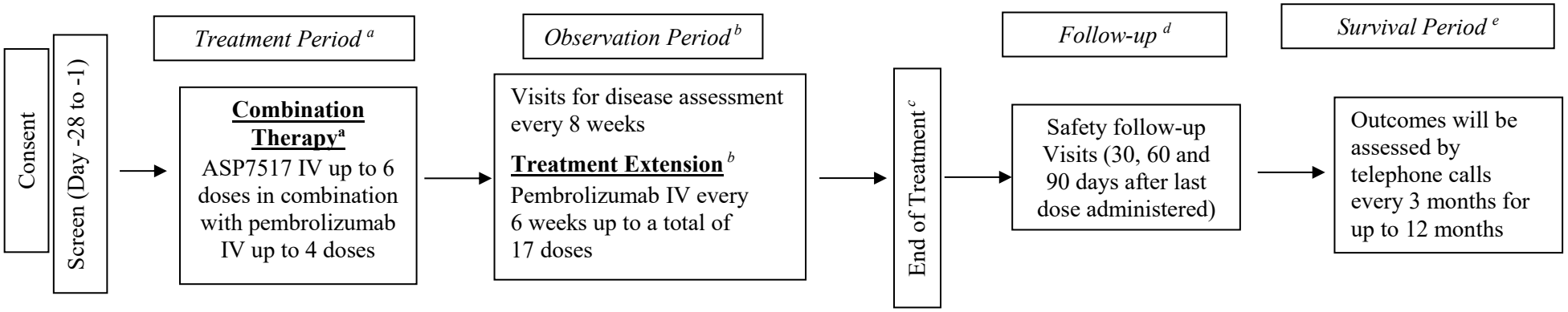
a. Participants receiving ASP7517 monotherapy will receive a single dose of ASP7517 per cycle for a total of 6 cycles with each cycle as 28 days.

b. EOT visit will be conducted for all participants after 7 days of EOT determination or prior to the initiation of new anticancer therapy, whichever occurs first. See footnote t in Table 1.

c. After the EOT visit, participants will complete 30-, 60- and 90-day safety follow-up visits from the last dose of ASP7517 or prior to the initiation of new anticancer therapy.

d. All participants will enter an observation period 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. Participants in the Observation Period will be followed for up to 48 weeks until iCPD (confirmed by independent central review), initiation of a new anticancer therapy or meeting 1 of the discontinuation criteria, whichever occurs first.

Figure 2 Combination Therapy: ASP7517 + Pembrolizumab



EOT: end of treatment; iCPD: "immune" confirmed progressive disease; IV: intravenous; iUPD: "immune" unconfirmed progressive disease; PR: partial response; q: every; SD: stable disease

a. In the combination treatment cohort, ASP7517 will be given on Day 1 of each 28-day cycle for up to 6 doses in combination with pembrolizumab administered every 6 weeks for up to 4 doses.

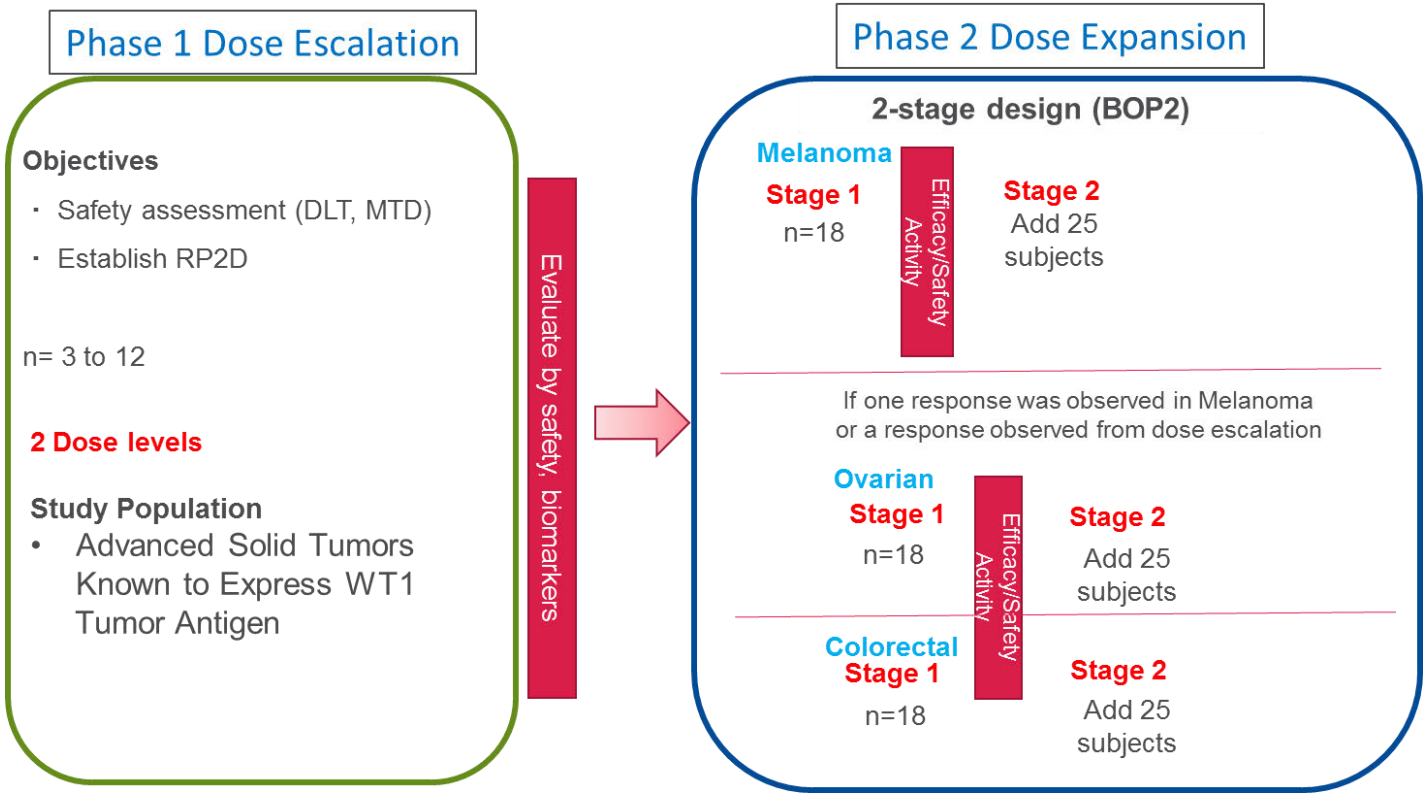
b. All participants will enter an observation period except those with iCPD, iUPD (per independent central review or local review) and who are not clinically stable or clinical progression is confirmed by the investigator. Participants completing the combination therapy treatment period who enter the Observation Period with PR, CR or SD are allowed to continue to receive pembrolizumab alone up to a total of 17 doses of pembrolizumab), for those participants who, in the opinion of the investigator, are continuing to derive clinical benefit. In addition, subsequent to the Treatment period, all participants, except those with iCPD, iUPD (per independent central review or local review) and who are not clinically stable or clinical disease progression is confirmed by the investigator, will enter the Observation Period to monitor treatment response for up to 78 weeks until iCPD (confirmed by independent central review), initiation of a new anticancer therapy or meeting 1 of the Observation Period discontinuation criteria, whichever occurs first. If participant discontinues combination treatment of ASP7517 at any time prior to C5D15, then the participant should continue observation period up to 96 weeks.

c. EOT visit will be conducted for all participants after 7 days of EOT determination or prior to the initiation of new anticancer therapy, whichever occurs first. See footnote s in Table 2.

d. After EOT visit, participants will complete 30-, 60- and 90-day safety follow-up visits from the last dose of pembrolizumab or prior to the initiation of new anticancer therapy.

e. All participants will be followed for survival and subsequent anti-cancer treatments following the conclusion of the Observation period. Outcomes will be assessed

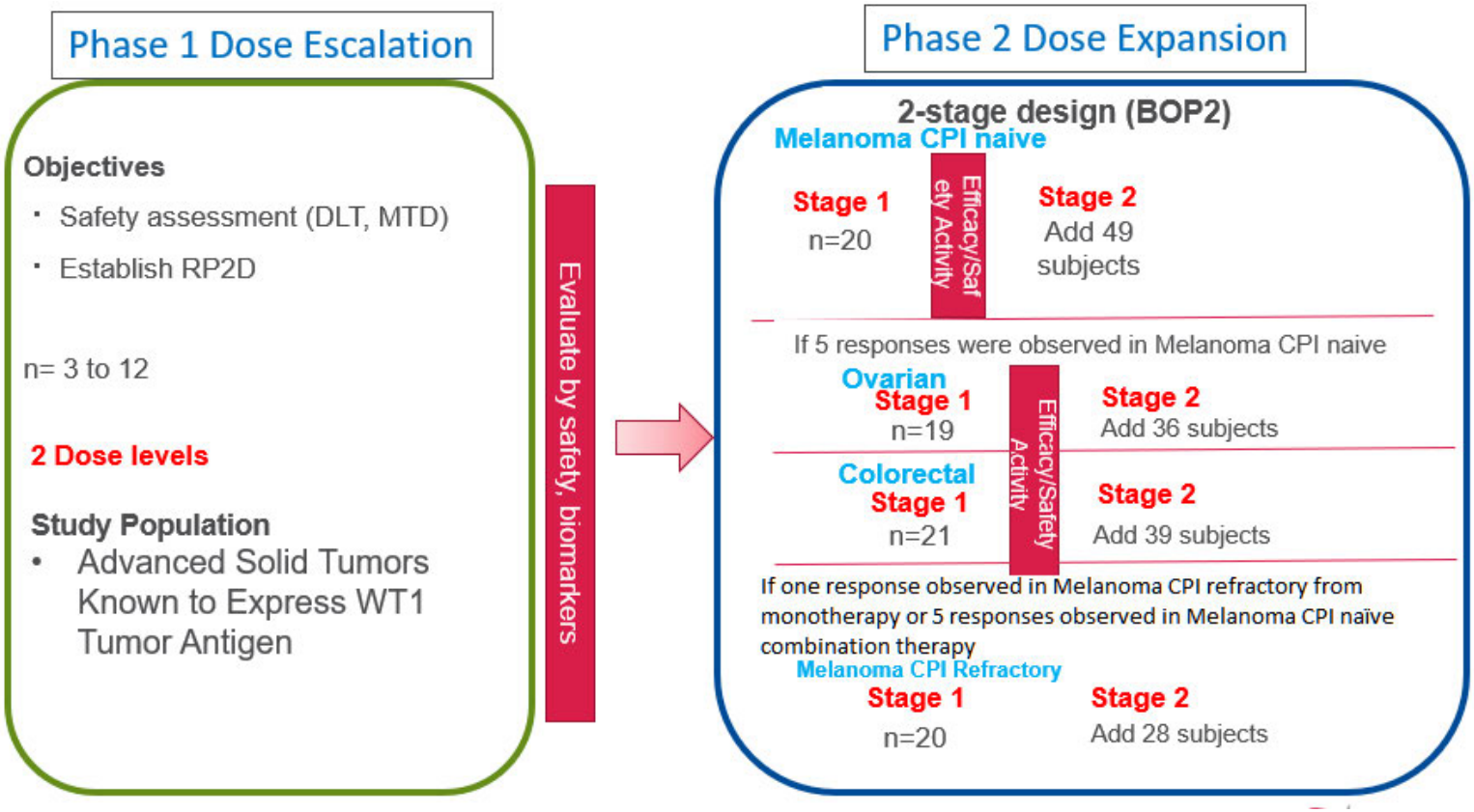
Figure 3 ASP7517 Monotherapy Arm



BOP2: Bayesian optimal phase 2; DLT: dose limiting toxicity; MTD: maximum tolerated dose; RP2D: recommended phase 2 dose; WT1: Wilms' tumor protein 1

Phase 1 Dose Escalation starting dose level of ASP7517 is 1×10^7 cells/dose, and the decision to escalate to the next dose level (1×10^8 cells/dose) will be made based in safety data review. Monotherapy dose expansion will be opened after the phase 1 monotherapy dose escalation has been completed.

Figure 4 Combination Therapy ASP7517 + Pembrolizumab Arm



BOP2: Bayesian optimal phase 2; CPI: checkpoint inhibitor; DESC: Dose Escalation and Safety Committee: DLT: dose limiting toxicity; MTD: maximum tolerated dose; RP2D: recommended phase 2 dose; WT1: Wilms' tumor protein 1

Phase 1 Dose Escalation starting dose level of ASP7517 is 1×10^7 cells/dose in combination and pembrolizumab, and the decision to escalate to the next dose level (1×10^8 cells/dose) will be made by the DESC. Combination therapy dose expansion will be opened after the phase 1 combination therapy dose escalation has been completed.

1.3 Schedules of Assessments

Table 1 Schedule of Assessments – Dose Escalation Cohort

	Scr	Treatment[a]																EOT[t]
		Cycle 1					Cycle 2					Cycles 3–4[b]			Cycles 5–6[c]			
Visit Days	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Window(days)		0	0	0	±1	±1	±1	0	±1	±1	±1	±3	±1	±1	±3	±1	±1	+7
Signed ICF	X																	
Medical and Disease History	X																	
Physical Examination[d]	X[d]	X[d]	X	X	X	X	X[d]	X	X	X	X	X[d]	X	X	X[d]	X	X	X[d]
Vital Signs	X	X[e]	X	X	X	X	X[e]	X	X	X	X	X[e]	X	X	X[e]	X	X	X
ECOG Performance	X	X[f]	X	X	X	X	X[f]		X	X	X	X[f]	X	X	X[f]	X	X	X
Chest X-ray	X[g]																	
12-Lead ECG[h]	X	X[h]				X	X[h]			X	X[h]	X[h]			X[h]			X
Prior and Concomitant Medications	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test for WOCBP	X[j]	X[j]					X[j]					X[j]			X[j]			X[j]
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[k]	X	X[f]	X	X	X	X	X[f]	X	X	X	X	X[f]	X	X	X[f]	X	X	X
Coagulation Profile (PT/INR, D-dimer, fibrinogen)[k]	X	X[f]	X	X	X	X	X[f]	X	X	X	X	X[f]			X[f]			X
Thyroid Profile Panel[l]	X	X									X	Every 6 weeks						X
IRT Transaction Required	X	X[m]					X					X			X			
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table continued on next page

Footnotes

	Scr	Treatment[a]																EOT[t]
		Cycle 1					Cycle 2					Cycles 3–4[b]			Cycles 5–6[c]			
Visit Days	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Window(days)		0	0	0	±1	±1	±1	0	±1	±1	±1	±3	±1	±1	±3	±1	±1	+7
PGx[n]		X[n]																
Buccal Swab for HLA Typing		X[f]																
Pharmacokinetic: A7517[o]		X	See Table 6 for detailed sample time points															X
Pharmacokinetic: Pembrolizumab[o]		X	See Table 6 for detailed sample time points															X
Anti-WT1 antibody		X[f]					X[f]					X[f]			X[f]			X
Immune Response Biomarker (ELISpot)		X[f]			X	X	X[f]			X	X	X[f]	X	X	X[f]	X	X	X
Immune Response Biomarker (Tetramer)		X[f]				X	X[f]				X	X[f]		X	X[f]		X	X
Immune Cell Phenotyping		X[f]			X	X	X[f]			X	X	X[f]	X	X	X[f]	X	X	X
Cytokines		X[f]	X	X	X	X	X[f]	X	X	X	X	X[f]	X	X	X[f]	X	X	X
Circulating Tumor DNA		X[f]					X[f]					X[f]			X[f]			X
Archival Tumor Tissue[p]		X																
Radiographic Disease Assessment[q]	X	Every 56 ± 7 days																
ASP7517 Dosing[r]		X					X					X			X			
Pembrolizumab Dosing[s]		X									X[s]	Every 6 weeks[s]						

AE: adverse event; C: Cycle; CR: complete response; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EOT: end of treatment; FFPE: formalin-fixed, paraffin-embedded; HLA: human leukocyte antigen; ICF: informed consent form; IP: investigational product; IRT: interactive response technology; MRI: magnetic resonance imaging; PGx: pharmacogenomic; PR: partial response; PT/INR: prothrombin time/international normalized ratio; SAE: serious adverse event; Scr: screening; SD: stable disease; WOCBP: woman of childbearing potential; WT1: Wilms' tumor 1 protein.

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a. Cycles 1 through 6 represent ASP7517 monotherapy or combination of ASP7517 and pembrolizumab therapy; each cycle is 28 days.

b. After the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as radiological response or SD, or reduction of disease-related symptoms) will continue further treatment of ASP7517 in Cycles 3 and 4, as decided by the investigator.

c. After the first 4 cycles, participants who achieve PR or SD may receive 2 doses of ASP7517 in Cycles 5 and 6.

d. Height measurement performed at screening only. Height measurement may be performed at a subsequent visit if it was not done at screening. Weight measurement performed at screening and Day 1 of each cycle.

e. The following vital sign assessment schedules apply:

- At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, vital signs are obtained predose (-1 h from start of pembrolizumab infusion), within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion, at the end of the pembrolizumab infusion (-5 to +10 min window), 30 min (± 10 min) after completion of the pembrolizumab infusion, within 15 min prior to the start of the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to +10 min window), and postdose (+30 min, +1, +2, +3 and +4 h [± 10 min window each] from end of the ASP7517 infusion).
- ASP7517 dosing only: Vital signs will be obtained within 15 min prior to start of the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to + 10 min window), as well as 30 min (± 5 min), 1 h (± 10 min) and 2 h (± 10 min) after completion of the ASP7517 infusion. If participants are still available, additional optional vital sign assessments 3 h (± 10 min) and 4 h (± 10 min) after completion of the ASP7517 infusion will be obtained.
- Pembrolizumab dosing only: Vital signs will be obtained within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion (-5 to + 10 min window), at the end of the pembrolizumab infusion (-5 to + 10 min window) and at 30 min (± 10 min) after completion of the pembrolizumab infusion for participants in the combination therapy.

f. Obtain predose.

g. If chest X-ray is performed within to 2 weeks of screening (prior to ICF and performed as part of standard of care), then it does not need to be repeated.

h. 12-lead ECGs will be recorded in triplicate (at least 2 min apart per time point) and transmitted electronically for central reading. ECGs may be repeated once during screening. On IP administration days, ECGs will be obtained:

- At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of ASP7517.
- ASP7517 dosing only: ECGs are obtained predose (-1 h from start of ASP7517 infusion) and 1 to 2 h post dose of ASP7517.
- Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.

i. Includes medications taken within 28 days prior to C1D1. Include all anticancer treatment received 28 days prior to IP administration.

j. Urine or serum pregnancy test will be performed in WOCBP. On treatment visit days, test must occur prior to IP administration.

k. Laboratory tests will be analyzed by the institution's local laboratory. However, sample results must also be submitted for centralized data entry. Laboratory test may be repeated during the screening period.

Footnotes continued on next page

l. Thyroid panel including triiodothyronine or free triiodothyronine, free thyroxine and thyroid stimulating hormone will be measured prior to receiving pembrolizumab only for participants in the combination cohort (C1D1, C2D15, C4D1 and C5D15). If the thyroid panel is to be measured on same day of pembrolizumab dosing (ex. C4D1, pembrolizumab monotherapy dosing visit), the thyroid panel must be measured prior to receiving pembrolizumab. Thyroid panels assessed on C1D1 and C2D15 only apply for the combination therapy cohort.

m. Enrollment or randomization will be done via IRT system after confirmation of eligibility and prior to dosing.

n. Whole blood for optional PGx study may be collected at C1D1 prior to IP administration.

o. See Table 6 for collection schedule for ASP7517 monotherapy and ASP7517 and pembrolizumab combination therapy.

p. Archival tumor specimen at a minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 20 FFPE unstained serial slides are required.

q. Same technique (CT/MRI) used at screening should be utilized throughout the study. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the participant's disease. Scans performed prior to informed consent as standard of care are acceptable as screening scans, if done within 28 days prior to C1D1.

r. In both the monotherapy and combination cohorts, each participant must remain at the site facility for 4 h following the participant's first dose of ASP7517. For the next dose (2^{nd} dose) or additional subsequent monotherapy with ASP7517, participants must remain at the site facility for at least 2 h after ASP7517 dosing.

s. In the combination therapy arm, pembrolizumab will be administered as an intravenous infusion over 30 min followed by ASP7517 administration at least 1 h after pembrolizumab administration.

t. If the participant will discontinue treatment due to meeting protocol criteria of CR after completion of Cycle 4 or a participant completes all 6 cycles of ASP7517, then all visits in the treatment cycle should be completed and the EOT visit will be performed 7 days (+ up to a 7-day window) after the last planned visit.

- If participant has CR after completing Cycle 4, the EOT visit would be performed between C4D22 and C4D29.
- If participant has SD or PR after completing Cycle 4, they are expected to complete all visits through C6D15 and the EOT visit would be performed between C6D22 and C6D29.
- If the investigator decides to discontinue treatment prior to the completion of any cycle, the EOT visit will occur 7 days after the decision to discontinue treatment.
- If new anticancer therapy is to be initiated, the EOT visit must occur prior to start of the new therapy, even if < 7 days from the decision to discontinue treatment.
- For combination therapy participants that continue with pembrolizumab monotherapy, EOT visit will be performed 7 days after 17th dose of pembrolizumab or 7 days after decision to discontinue treatment, or prior to start of new anticancer therapy, whichever is earliest.

Table 2 Schedule of Assessments for Dose Expansion Cohort

	Scr (-28 to -1)	Treatment[a]												EOT[s]
		Cycle 1				Cycle 2				Cycles 3–4[b]		Cycles 5–6[c]		
		1	4	8	15	1	4	8	15	1	15	1	15	+7
Window(days)		0	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	
Signed ICF	X													
Medical and Disease History	X													
Physical Examination[d]	X[d]	X[d]	X	X	X	X[d]	X	X	X	X[d]	X	X[d]	X	X[d]
Vital Signs	X	X[e]	X	X	X	X[e]	X	X	X	X[e]	X	X[e]	X	X
ECOG Performance	X	X[f]	X	X	X	X[f]	X	X	X	X[f]	X	X[f]	X	X
Chest X-ray	X[g]													
12-Lead ECG[h]	X	X[h]				X[h]				X[h]		X[h]		X
Prior and Concomitant Medications	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test for WOCBP	X[j]	X[j]				X[j]				X[j]		X[j]		X[j]
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[k]	X	X[f]		X	X	X[f]	X	X	X	X[f]	X	X[f]	X	X
Coagulation Profile (PT/INR, D-dimer, fibrinogen)[k]	X	X[f]		X	X	X[f]		X	X	X[f]	X	X[f]	X	X
Thyroid Profile Panel[l]	X	X							X	Every 6 weeks after C2D15 dose				X
PGx[m]		X[m]												
Buccal Swab for HLA Typing		X[f]												
AE/SAE Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic: A7517[n]		X	See Table 6 for sample time points											X
Pharmacokinetic: Pembrolizumab[n]		X	See Table 6 for sample time points											X
Anti-WT1 antibody		X[f]				X[f]				X[f]		X[f]		X

Table continued on next page

Footnotes

	Scr (-28 to -1)	Treatment[a]												EOT[s]
		Cycle 1				Cycle 2				Cycles 3–4[b]		Cycles 5–6[c]		
		1	4	8	15	1	4	8	15	1	15	1	15	+7
Window(days)		0	± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	
Immune Response Biomarker (ELISpot)		X[f]		X	X	X[f]		X	X	X[f]	X	X[f]	X	X
Immune Response Biomarker (Tetramer)		X[f]			X	X[f]			X	X[f]	X	X[f]	X	X
Immune Cell Phenotyping		X[f]		X	X	X[f]		X	X	X[f]	X	X[f]	X	X
Cytokines		X[f]	X	X	X	X[f]	X	X	X	X[f]	X	X[f]	X	X
Circulating tumor DNA		X[f]				X[f]				X[f]		X[f]		X
Archival Tumor Tissue[o]		X												
Tumor Tissue, Fresh Biopsy		X[q]							X[r]					
Radiographic Disease Assessment[p]	X	Every 56 ± 7 days												
IRT Transaction Required	X	X[o]				X				X		X		
ASP7517 Dosing		X				X				X		X		
Pembrolizumab Dosing		X							X	Every 6 weeks after C2D15 dose				

AE: adverse event; C: Cycle; CR: complete response; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EOT: end of treatment; FFPE: formalin-fixed, paraffin-embedded; HLA: human leukocyte antigen; ICF: informed consent form; IP: investigational product; IRT: interactive response technology; MRI: magnetic resonance imaging; PGx: pharmacogenomic; PR: partial response; PT/INR: prothrombin time/international normalized ratio; SAE: serious adverse event; Scr: screening; SD: stable disease; WOCBP: woman of childbearing potential; WT1: Wilms' tumor 1 protein.

a. Cycles 1 through 6 represent ASP7517 monotherapy or combination of ASP7517 and pembrolizumab therapy; each cycle is 28 days.

b. After the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as radiological response or SD, or reduction of disease-related symptoms) will continue further treatment of ASP7517 as decided by the investigator.

c. After the first 4 cycles, participants who achieve PR or SD may receive 2 doses of ASP7517 in Cycles 5 and 6.

d. Height measurement performed at screening only. Height measurement may be performed at a subsequent visit if it was not done at screening. Weight measurement performed at screening and Day 1 of each cycle.

Footnotes continued on next page

e. The following vital sign assessment schedules apply:
   - At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, vital signs are obtained predose (-1 h from start of pembrolizumab infusion), within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of pembrolizumab infusion, at the end of pembrolizumab infusion (-5 to +10 min window), 30 min (± 10 min) after completion of the pembrolizumab infusion, within 15 min prior to start of ASP7517 infusion, every 15 min (-5 to +10 min window) during ASP7517 infusion, at the end of ASP7517 infusion (-5 to +10 min window), and postdose (+30 min, +1, +2, +3 and +4 h [± 10 min window each] from end of the ASP7517 infusion).
   - ASP7517 dosing only: Vital signs will be obtained within 15 min prior to start of the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to + 10 min window), as well as 30 min (± 5 min), 1 h (± 10 min) and 2 h (± 10 min) after completion of the ASP7517 infusion. If participants are still available, additional optional vital sign assessments 3 h (± 10 min) and 4 h (± 10 min) after completion of the ASP7517 infusion will be obtained.
   - Pembrolizumab dosing only: Vital signs will be obtained within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion, at the end of the pembrolizumab infusion (-5 to + 10 min window) and at 30 min (± 10 min) after completion of the pembrolizumab infusion for participants in the combination therapy.

f. Obtain predose.

g. If chest X-ray is performed prior to 2 weeks of screening (prior to ICF and performed as part of standard of care), then it does not need to be repeated.

h. During ASP7517 and pembrolizumab combination therapy, 12-lead ECGs will be recorded in triplicate (at least 2 min apart per time point) and transmitted electronically for central reading. After treatment with ASP7517 has been discontinued, 12-lead ECGs will be recorded as a single assessment (in triplicate if deemed necessary, at least 2 min apart per time point) and read locally. ECG may be repeated once during screening. On IP administration days, ECGs will be obtained:
   - At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose.
   - ASP7517 dosing only: ECGs are obtained predose (-1 h from start of ASP7517 infusion) and 1 to 2 h post dose of ASP7517.
   - Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.

i. Includes medications taken within 28 days prior to C1D1. Include all anticancer treatment received 28 days prior to IP administration.

j. Urine or serum pregnancy test will be performed in WOCBP. On treatment visit days, test must occur prior to IP administration.

k. Laboratory tests will be analyzed by the institution's local laboratory. However, sample results must also be submitted for centralized data entry. Laboratory test may be repeated during the screening period.

l. Thyroid panel including triiodothyronine or free triiodothyronine, free thyroxine and thyroid stimulating hormone will be measured prior to receiving pembrolizumab only for participants in the combination cohort (C1D1, C2D15, C4D1 and C5D15). If the thyroid panel is to be measured on same day of pembrolizumab dosing (ex. C4D1, pembrolizumab monotherapy dosing visit), the thyroid panel must be measured prior to receiving pembrolizumab.

m. Whole blood for optional PGx study may be collected at C1D1 prior to IP administration.

n. See Table 6 for collection schedule for ASP7517 monotherapy and ASP7517 and pembrolizumab combination therapy.

o. Archival tumor specimen at a minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 20 FFPE unstained serial slides are required.

Footnotes continued on next page

p. Same technique (CT/MRI) used at screening should be utilized throughout the study. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the participant's disease. Scans performed prior to informed consent as standard of care are acceptable as screening scans, if done within 28 days prior to C1D1.

q. Participants in all expansion cohorts are required to provide a tumor specimen obtained within 56 days prior to first dose of IP.

r. Participants in all expansion cohorts are required to provide an on-treatment tumor specimen collected ± 7 days of the C2D15 visit (or unscheduled) if predose biopsy is available and if medically feasible.

s. If the participant will discontinue treatment due to meeting protocol criteria of CR after completion of Cycle 4 or a participant completes all 6 cycles of ASP7517, then all visits in the treatment cycle should be completed and the EOT visit will be performed 7 days (+ up to a 7-day window) after the last planned visit.

- If participant has CR after completing Cycle 4, the EOT visit would be performed between C4D22 and C4D29.
- If participant has SD or PR after completing Cycle 4, they are expected to complete all visits through C6D15 and the EOT visit would be performed between C6D22 and C6D29.
- If the investigator decides to discontinue treatment prior to the completion of any cycle, the EOT visit will occur 7 days after the decision to discontinue treatment.
- If new anticancer therapy is to be initiated, the EOT visit must occur prior to start of the new therapy, even if < 7 days from the decision to discontinue treatment.
- For combination therapy participants that continue with pembrolizumab monotherapy, EOT visit will be performed 7 days after 17th dose of pembrolizumab or 7 days after decision to discontinue treatment, or prior to start of new anticancer therapy, whichever is earliest.

Table 3 Schedule of Assessments for Safety Follow-up, Observation Period and Survival Follow-up Period for Participants who End the Treatment Early or Completed the Treatment Period

Visit	Observation Period				Survival Follow-up
	Safety Follow-up[f]			Disease Assessment, Up to 48 weeks[a]	
	30 days from last dose	60 days from last dose	90 days from last dose	Visits every 8 weeks ± 1 week from last planned scan	Every 3 months
Window (days)	± 3	± 3	± 3		± 7
Physical Examination	X	X	X		
Vital Signs	X	X	X		
ECOG Performance	X	X	X		
Concomitant Medications	X	X	X	X	
12-Lead ECG	X	X	X		
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)	X	X	X	X	
Pregnancy Test for WOCBP	X	X	X		
AE/SAE Assessment	X	X	X	X	
Pharmacokinetic sample for cell kinetics (ASP7517)	See Table 6 for sample time points				
Blood Sample for anti-WT1 antibody	X	X	X	X[b]	
Blood Sample for Immune Response Biomarker (ELISpot)	X	X	X	X[c]	
Blood Sample for Immune Response Biomarker (Tetramer)	X	X	X	X[b]	
Blood Sample for Immune Cell Phenotyping	X	X	X	X[c]	
Blood Sample for Cytokines	X	X	X	X[c]	
Blood Sample for ctDNA	X	X	X	X[d]	
Radiographic Disease Assessment				X	
Survival Follow-up[e]					X

AE: adverse event; ctDNA: circulating tumor DNA; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EOT: end of treatment; iCPD: "immune" confirmed progressive disease; iUPD: unconfirmed disease progression disease based on iRECIST; SAE: serious adverse event; WOCBP: woman of childbearing potential; WT1: Wilms' tumor 1 protein.

Footnotes continued on next page

a. For participants in ASP7517 monotherapy treatment arm. Participants in the Observation period will be followed until iCPD, iUPD who are not clinically stable, clinical disease progression, initiation of a new anticancer therapy or for a total of up to 48 weeks starting at EOT, whichever occurs first.
b. Maximum of 8 samples collected during the Observation Period. Sample will be collected at the time of the disease assessment visit.
c. Maximum of 4 samples collected during the Observation Period. Sample will be collected at the time of the disease assessment visit.
d. Sample will be collected only at the time of discontinuation due to disease progression.
e. Outcomes will be assessed by telephone calls every 3 months for up to 12 months.
f. In Monotherapy Arm, Safety Follow-up is a part of 48 weeks of Observation period. Observation period starts after EOT.

Table 4 Schedule of Assessments for Observation Period, Safety Follow-up and Survival Follow-up for Participants who Receive Pembrolizumab Monotherapy in the Observation Period

Visit	Observation Period Up to 96 weeks[a]	Safety Follow-up			Survival Follow-up
	Visits every 6 weeks (± 1 week) from last Pembrolizumab dose during combination treatment	30 days from last dose	60 days from last dose	90 days from last dose	Every 3 months
Window (days)		± 3	± 3	± 3	± 7
Physical Examination	X	X	X	X	
Vital Signs	X[b]	X	X	X	
ECOG Performance		X	X	X	
Concomitant Medications	X	X	X	X	
12-Lead ECG	X[c]	X	X	X	
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)	X[c]	X	X	X	
Thyroid Profile Panel (triiodothyronine or free triiodothyronine, free thyroxine and thyroid stimulating hormone)	X[c]	X[c]			
Pregnancy Test for WOCBP	X[c]	X	X	X	
AE/SAE Assessment	X	X	X	X	
Pharmacokinetic samples for cell kinetics (ASP7517)	See Table 6 for schedule				
Pharmacokinetic sample for pembrolizumab	See Table 6 for schedule				
Blood Sample for anti-WT1 antibody	X[c,h]				
Blood Sample for Immune Response Biomarker (ELISpot)	X[c,g]				
Blood Sample for Immune Response Biomarker (Tetramer)	X[c,h]				
Blood Sample for Immune Cell Phenotyping	X[c,g]				
Blood Sample for Cytokines	X[c,g]				
Blood Sample for ctDNA	X[c,f]				
Radiographic Disease Assessment	X[d]				
Pembrolizumab Dosing	X[e]				
Survival Follow-up[i]					X

AE: adverse event; C5D15: Cycle 5 Day 15; CR: complete response; ctDNA: circulating tumor DNA; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; iCPD: "immune" confirmed progressive disease; iUPD: unconfirmed disease progression disease based on iRECIST; PR: partial response; SAE: serious adverse event; SD: stable disease: WOCBP: woman of childbearing potential; WT1: Wilms' tumor 1 protein.

Footnotes continued on next page

a. For participants in ASP7517 and pembrolizumab treatment who have achieved CR, PR or SD and receiving pembrolizumab monotherapy. Pembrolizumab will be administered every 6 weeks for up to a total of 17 doses. Participants in the Observation period will be followed until iCPD, iUPD who are not clinically stable, clinical disease progression, initiation of a new anticancer therapy or for a total of up to 96 weeks, whichever occurs first. If participant discontinues pembrolizumab at any time during the 78-week Observation period, the participant will continue with Safety Follow-up visits, then resume Observation period visits every 6 weeks until iCPD, iUPD who are not clinically stable, clinical disease progression, initiation of a new anticancer therapy or for a total of up to 78 weeks from last dose of ASP7517, whichever occurs first. If participant discontinues combination treatment of ASP7517 at any time prior to C5D15, then the participant should continue observation period up to 96 weeks.
b. Vital signs should be obtained prior to pembrolizumab infusion and within 30 min (± 10 min window) after completion of pembrolizumab infusion.
c. Obtained predose.
d. Disease assessment every 8 weeks.
e. Pembrolizumab administered every 6 weeks for up to 17 doses total (for the study) for those participants who, in the opinion of the investigator, are continuing to derive clinical benefit.
f. Sample collected at the time of discontinuation due to disease progression.
g. Sample collected at the time of pembrolizumab administration of doses 5 and 7 (i.e., 2 samples are collected from the time the participant enters the Observation Period).
h. Sample collected at the time of pembrolizumab administration of doses 5, 7, 9, 11 and 13 (i.e., 5 samples are collected from the time the participant enters the Observation Period).
i. Outcomes will be assessed by telephone calls every 3 months for up to 12 months, starting from the 90-day safety follow-up or last visit prior to the start of new anti-cancer therapy.

Table 5 Schedule of Replication Competent Lentivirus for Dose Escalation Cohort and Dose Expansion Cohort

Assessment	C1D1	3 Months After Treatment Initiation or at End of Treatment, Whichever is First	6 Months after Treatment Initiation	12 Months after Treatment Initiation	18 Months after Treatment Initiation
Window	0	± 7 days	± 1 month	± 1 month	+1 month
Blood Sample for RCL[a]	X[b]	X	X	X	X

C1D1: Cycle 1 Day 1; RCL: replication competent lentivirus

a. If there are positive results, additional follow-up assessments may be required. Refer to [Section 7.7.1].

b. Obtained predose.

Table 6 Sample Collection Schedule-Dose Escalation Cohort and Dose Expansion Cohort

Cycle	Day	Time Point	Window	Dose Escalation		Dose Expansion	
				Pembrolizumab PK[h]	ASP7517 PK	Pembrolizumab PK[h]	ASP7517 PK
Cycle 1	1	Predose	- 60 min[a]	X	X	X	X
		End of pembrolizumab Infusion	+ 15 min[b]	X		X	
		End of ASP7517 Infusion	+ 15 min[c]		X		X
		30 min post ASP7517 Infusion	± 15 min		X		X
		1 h post ASP7517 Infusion	± 15 min		X		X
		2 h post ASP7517 Infusion	± 15 min		X		X
		5 h post ASP7517 Infusion	± 15 min		X		X
	2	24 h post ASP7517 Infusion	± 60 min		X		
Cycle 2	1	Predose	- 60 min[d]		X		X
		End of ASP7517 Infusion	+ 15 min[c]		X		X[g]
		30 min post ASP7517 Infusion	± 15 min		X		X[g]
		1 h post ASP7517 Infusion	± 15 min		X		X[g]
		2 h post ASP7517 Infusion	± 15 min		X		X[g]
		5 h post ASP7517 Infusion	± 15 min		X		X[g]
	2	24 h post ASP7517 Infusion	± 60 min		X		
	15	Predose	- 60 min[a]	X			
		End of pembrolizumab Infusion	+ 15 min[b]	X			
Cycle 3	1	Predose	- 60 min[d]		X		
		End of ASP7517 Infusion	+ 15 min[c]		X		
Cycle 4	1	Predose	- 60 min[a]	X	X	X[g]	X[g]
		End of pembrolizumab Infusion	+ 15 min[b]	X		X[g]	
		End of ASP7517 Infusion	+ 15 min[c]		X		X[g]
		30 min post ASP7517 Infusion	± 15 min		X		
		1 h post ASP7517 Infusion	± 15 min		X		
		2 h post ASP7517 Infusion	± 15 min		X		
		5 h post ASP7517 Infusion	± 15 min		X		

Table continued on next page

Cycle	Day	Time Point	Window	Dose Escalation		Dose Expansion	
				Pembrolizumab PK[h]	ASP7517 PK	Pembrolizumab PK[h]	ASP7517 PK
Cycle 5	1	Predose	- 60 min[d]		X		
		End of ASP7517 Infusion	+ 15 min[c]		X		
	15	Predose	- 60 min[a]	X			
		End of pembrolizumab Infusion	+ 15 min[c]	X			
Cycle 6	1	Predose	- 60 min[d]		X		
		End of ASP7517 Infusion	+ 15 min[c]		X		
EOT	EOT	-	-	X	X	X	X
Safety Follow-up[e]	30 days	NA	-		X		
Observation Period Pembrolizumab Monotherapy: Doses 5 and 6[f]	1	Predose	- 60 min[a]	X	X	X	
		End of pembrolizumab Infusion	+ 15 min[b]	X		X	

CR: complete response; EOT: end of treatment; NA: not applicable; PK: pharmacokinetics; .

a. Within 60 min prior to pembrolizumab infusion.

b. Within 15 min after the end of pembrolizumab infusion (before the infusion of ASP7517 on C1D1 and C4D1).

c. Within 15 min after the end of ASP7517 infusion.

d. Within 60 min prior to ASP7517 infusion.

e. For participants in ASP7517 monotherapy arm and participants in ASP7517 and pembrolizumab combination therapy arm who end the treatment early or completed the treatment period [see Table 3].

f. For participants in ASP7517 and pembrolizumab combination therapy arm who receive pembrolizumab monotherapy in the Observation Period [see Table 4]. Doses 5 and 6 are the first 2 doses of pembrolizumab in the Observation Period when 6 cycles in the Treatment Period are completed. If the Treatment Period ends earlier than Cycle 6 and pembrolizumab monotherapy continues in the Observation Period, pembrolizumab PK is continued to the 6th dose of pembrolizumab from C1D1.

g. Sample not collected in Stage 2 of Dose Expansion.

h. Pembrolizumab PK samples only applicable for participants in the combination therapy arm.

2 INTRODUCTION

In this study (7517-CL-1101), ASP7517 is indicated as a single agent and in combination with pembrolizumab in participants with advanced solid tumors known to express the Wilms' tumor protein 1 (WT1) antigen.

Details about ASP7517 are provided in the Investigator's Brochure.

Details about pembrolizumab are provided in the summary of product characteristics/package insert of this product.

2.1 Study Rationale

Accumulating evidence indicates that the WT1 gene plays an oncogenic function in leukemogenesis and tumorigenesis. The WT1 gene is highly expressed in leukemia and various types of solid tumors (e.g., melanoma, ovarian cancer and colon cancer) and is listed at the top of the ranking of tumor antigen [Sugiyama, 2010]. In addition, WT1 tumor antigen expression plays an important role in the progression of disease and prognosis of human malignancies [Qi, 2015; Sugiyama, 2010]. ASP7517 has effects against WT1 expressing tumors by inducing both natural killer cell activity (innate immunity) and WT1-specific T cell dependent antitumor effects (adaptive immunity). Nonclinical studies were performed to demonstrate that both the innate and adaptive immune systems were activated by artificial Adjuvant Vector Cell (aAVC). In addition, nonclinical data suggest that ASP7517 is active in WT1 expressing tumor as described in Sections 4.1.1.2.5, 4.1.1.2.6 and 4.1.1.2.7 of the Investigator's Brochure; therefore, ASP7517 treatment for solid tumors known to express WT1 may result in clinical benefit.

2.2 Background

The WT1 gene was isolated as the gene responsible for a childhood renal neoplasm, Wilms' tumor, which was thought to arise as a result of inactivation of both alleles of the WT1 gene located at chromosome 11p13 [Gessler et al, 1990]. This gene encodes a zinc finger transcription factor that plays an important role in cell growth and differentiation [Sugiyama, 2001].

The WT1 gene is also expressed at high levels in almost all types of solid tumors, with its expression level serving as a significant prognostic factor. Cancers over-expressing WT1 include melanoma, leukemia, breast cancer, ovarian cancer, glioblastoma, soft tissue sarcoma and colorectal cancer (CRC) [Bejrananda et al, 2010; Wagner et al, 2008; Nakatsuka et al, 2006; Miyoshi et al, 2002; Menssen et al, 2000; Oji et al, 1999; Miwa et al, 1992].

In addition to its prognostic role in a variety of cancer types [Köbel et al, 2008; Sotobori et al, 2006], WT1 is recognized as a promising target for immunotherapy based on its unique features [Dao et al, 2013; Cheever et al, 2009]. In addition, WT1 tumor antigen expression plays an important role in the disease progression of human malignancies [Qi, 2015; Sugiyama, 2010].

ASP7517 has effects against WT1-expressing tumors by inducing both natural killer (NK) cell activity (innate immunity) and WT1-specific T cell-dependent antitumor effects (adaptive immunity).

Nonclinical pharmacology studies were performed to demonstrate that both the innate and adaptive immune system were activated by aAVC. Activation of innate immunity was demonstrated in a mouse lung metastatic cancer model, where NK cell depletion resulted in reduced antitumor effects. Activation of adaptive immunity was demonstrated in a second mouse model where mice were inoculated with AML tumor cells that either expressed WT1 or did not express WT1. In this model, aAVC (NIH3T3)-WT1 (ASP7517 surrogate) prolonged survival in the mice inoculated with the WT1-expressing tumor cells. In addition, studies of ASP7517 surrogate demonstrated increase of the production of CD8+ T cells secreting IFNγ by WT1 peptide stimulation. For additional information on ASP7517 please refer to Investigator's Brochure.

2.2.1 Melanoma

Overall survival for advanced-stage melanoma of the skin has improved dramatically over the last decade from approximately 9 months before 2011 to at least 2 years in 2017 [Luke et al, 2017]. However, approximately 60% to 70% of patients that receive anti-programmed cell death protein 1 (anti-PD-1) therapy do not respond to treatment. Furthermore, acquired resistance is common, causing some patients who initially responded to the therapy to later experience disease progression. A recent study found that nearly 25% of patients with melanoma who initially had received an objective response had disease recurrence at follow-up (a median of 21 months) [Simeone & Ascierto, 2017]. Therefore, there is a high unmet need that persists for this patient population.

2.2.2 Colorectal Cancer

CRC is one of the leading causes of cancer-related deaths worldwide [Fitzmaurice et al, 2017]. Nearly 20% of CRC patients have metastasis at diagnosis [Christensen et al, 2018]. The treatment is palliative in the majority of these patients and the goal of treatment is to increase the quality of life and prolong overall survival (OS) [Weeks et al, 2012]. Stage 4 CRC has a poor prognosis, with a less than 10% 5-year survival rate and a median survival time of approximately 5 months in patients who receive optimal supportive care without chemotherapy [Zacharakis et al, 2010]; and a 5-year survival rate less than 20% with chemotherapy, presenting the need of new therapy to address the high unmet need that persists for this patient population [American Cancer Society 2020; Siegel et al, 2014].

2.2.3 Ovarian Cancer

Ovarian cancer is predominantly diagnosed in postmenopausal women, and due to the lack of symptoms in early stages, 75% of patients are diagnosed in advanced stages of the disease [Doubeni et al, 2016]. Most patients diagnosed with advanced ovarian cancer develop platinum resistant/refractory disease [Matsuo et al, 2010]. The median progression-free survival time for recurrent ovarian cancer is less than 6 months, and median overall survival is less than 15 months [Shimokawa et al, 2018]. Recurrent epithelial ovarian carcinoma is

generally considered an incurable disease and second-line chemotherapy may be administered for palliation of symptoms and extension of survival [Adams et al, 1998; Ozols, 1997].

Based on the above, the majority of patients with melanoma, CRC and ovarian cancer are not cured with available therapies, underscoring the urgent need for new therapeutic alternatives that will improve the clinical outcomes of these patients.

This study will include participants with locally progressive (unresectable) or metastatic solid tumor malignancies known to express WT1 antigen, including but not limited to melanoma, ovarian cancer and CRC, who have received all standard therapies (except CPI-naïve melanoma in phase 2). This study may contribute to an unmet medical need.

2.3 Risk/Benefit Assessment

2.3.1 ASP7517 Risk Assessment

One study with ASP7517 in humans is currently ongoing (7517-CL-0101). The potential risks described in Table 7 and sections below are based on ASP7517 nonclinical studies. Also, study 7517-CL-0101 and clinical data from compounds with similar mechanism of action or composition risks information is available and discussed in this section.

The management of toxicities should be based on institutional standard of care, published guidelines, as well as on investigator judgment, the protocol instructions regarding risk monitoring, and interruption or discontinuation of investigational product (IP) treatment.

In the first-in-human ongoing clinical study (7517-CL-0101), there have been no dose limiting toxicities (DLTs) and 15 serious adverse events (SAE; 11 febrile neutropenia, 1 pneumonia fungal, 1 atrial fibrillation, 1 delirium and 1 tumor-associated fever) reported (Data Snapshot/Extraction Point 31 May 2021). All reported SAEs were assessed as unrelated to the study product.

Table 7 Potential Safety Concerns of ASP7517 based on Preclinical Studies

Key Safety Targets	Key Observations	Relevance to Human Usage
Liver	Increased liver weight, increased AST and ALT, hepatocyte focal necrosis, mixed inflammatory cell infiltration ($\geq 1 \times 10^5$ cells/kg, mononuclear cell aggregation ($\geq 1 \times 10^6$ cells/kg, pigment laden macrophage infiltration (at $\geq 1 \times 10^7$ cells/kg)	Potential risk
Spleen	Increased spleen weight (at $\geq 1 \times 10^5$ cells/kg); extramedullary hematopoiesis ($\geq 1 \times 10^6$ cells/kg)	Potential risk
Emboli	Emboli in the spleen and liver ($\geq 1 \times 10^5$ cells/kg)	Potential risk
Kidney	Increased creatinine, tubular basophilia, mononuclear cell infiltration ($\geq 1 \times 10^6$ cells/kg)	Potential risk
Hematology	Decreased platelet count 1 day after dose, increased platelet count 7 days after dose ($\geq 1 \times 10^5$ cells/kg)	Potential risk
Pancreas	Acinar cell necrosis, interstitial edema, mononuclear cell infiltration ($\geq 1 \times 10^7$ cells/kg)	Potential risk
Urinary bladder	Mononuclear cell infiltration (1×10^8 cells/kg)	Low potential risk
Submandibular gland	Mononuclear cell infiltration (1×10^8 cells/kg)	Low potential risk
Epididymis	Interstitial fibrosis and granuloma (1×10^8 cells/kg)	Low potential risk
Tumorigenicity	No colony formation in soft agar test No human cells (ASP7517) detected within 2 weeks in NOG mice after a dose of 1×10^8 cells/kg	Low potential risk
Embryo-fetal development	No embryo-fetal development studies have been performed to date	Not determined

ALT: alanine aminotransferase; AST: aspartate aminotransferase; NOG: NOD.Cg-Prkdc^{scid} Il2rg^{tm1Sug}/Jic.

2.3.1.1 Liver

Preclinical studies demonstrated that liver could be the target organ of toxicity for ASP7517, which is related to the activation of an innate immune response by presenting α-GalCer linked to CD1d on the surface of ASP7517 to natural killer T (NKT) cells. The activation of NKT cells is thought to be responsible for the hepatic injury induced with ASP7517. The hepatic findings could be monitored (increased aspartate aminotransferase [AST] and alanine aminotransferase [ALT] 1 day after administration) and were completely reversed by 28 days after ASP7517 administration. The AEs in mice included increased liver weight, AST and ALT elevation, embolus, hepatocyte focal necrosis, mixed inflammatory cell infiltration, microgranuloma, granulomatous inflammation, mononuclear cell aggregation and pigment laden macrophage infiltration. Close monitoring of liver function and toxicities is required during clinical studies.

2.3.1.2 Hematology

A dose-related decrease in platelet count was noted 1 day after the first dose. There was also a dose related decrease in platelet count following the second dose. Platelet counts were increased above baseline 7 days after the first and second dose, and recovered to normal

physiological ranges by day 28. The standard assessment of hematology is recommended in clinical studies.

2.3.1.3 Pancreas

Edema was noted in gross pathology at doses of 1×10^7 cells/kg and higher doses 1 day after the sixth dose. This finding fully resolved by 7 or 28 days after the sixth dose. Histological assessment showed the presence of focal necrosis at a dose of 1×10^8 cells/kg 7 days after the second dose. After the sixth dose, acinar cell necrosis and interstitial edema on 1 day, and mononuclear cell infiltration and focal acinar cell necrosis on 7 days, were observed at 1×10^7 cells/kg and higher doses. No edema or cell necrosis was observed 28 days after the sixth dose.

The no-observed-adverse-effect-level for the toxicity in the pancreas was 1×10^6 cells/kg. These findings were partially or fully resolved 28 days after the second or the sixth dose.

2.3.1.4 Kidney

Increased serum creatinine was seen 1 day after the first dose. This finding was completely resolved 7 days after the first dose. In addition, histological assessment showed basophilic tubules and infiltration of mononuclear cells 7 days after the second dose. These histological findings were completely resolved 28 days after the second dose. The presence of basophilic tubules is interpreted as regeneration of renal tubules. The standard monitoring of kidney function parameters (creatinine, blood urea nitrogen) is recommended in clinical studies.

2.3.1.5 Spleen

Spleen weights were increased 1 day after the first and second dose and showed a trend toward recovery in 28 days. In addition, histological assessments showed apoptosis in lymphoid follicle of the spleen 1 day after the first or second dose. This finding was completely resolved by 7 days after ASP7517 administration. Also, emboli were observed in the spleen 1 day after administering the first and second dose of ASP7517 and resolved completely by 7 days of dosing.

In addition, lymphoid follicular hyperplasia was noted 7 days after the first or second dose that increased in incidence and severity with dose increase, whereas it had not been observed 1 day after the first and second doses. This finding was partially or completely resolved by 28 days post dosing. Standard hematology testing is recommended in clinical studies.

2.3.1.6 Infusion-related Reactions

In nonclinical studies with ASP7517, IRRs/cytokine-release syndrome (CRS) was not seen. However, there are potential toxicities with intravenous infusion immunotherapy and the exact mechanism causing standard infusion reactions is unclear, but most reactions appear to arise from cytokine release from immune-mediated mechanisms [Lee et al, 2014].

The symptoms and signs associated with a standard infusion reaction include fever, shaking chills, flushing and/or itching, changes in heart rate and blood pressure, shortness of breath or chest discomfort, pain in back or abdomen, nausea, vomiting and/or diarrhea and skin rash.

In addition to the signs and symptoms associated with a standard infusion reaction, CRS may result in neurologic signs and symptoms such as mental status changes, confusion and delirium. Renal and hepatic manifestations may include azotemia, elevated transaminases and hyperbilirubinemia, respectively. Coagulation parameters may also be affected and manifested by elevated D-dimer and hypofibrinogenemia, with or without bleeding. In addition, tumor lysis syndrome may also be associated with CRS [Lee et al, 2014]. Participants should be closely monitored for IRRs and CRS and appropriately managed per standard of care.

2.3.1.7 Allergic Reactions and Anaphylaxis

Based on the nonclinical data, no signs or symptoms of allergic reaction or anaphylaxis were seen following ASP7517 administration. The signs and symptoms of anaphylaxis overlap with those of standard infusion reactions. However, certain features are highly suggestive of anaphylaxis, such as urticaria, repetitive cough, wheeze, throat tightness and change in voice, angioedema (usually of face, eyelids or lip), hypotension, loss of consciousness, nausea, vomiting, abdominal cramping and diarrhea. Participants should be monitored closely for any signs or symptoms of allergic reaction or anaphylaxis and managed appropriately per standard of care.

2.3.1.8 Other

AEs reported from solid tumor, early phase clinical trials using α-GalCer based immunotherapies include: fever, headache, fatigue, dizziness, chest pain, lymphopenia, hot flash, hyperkalemia, lactate dehydrogenase increase, creatinine increase, anemia, increased cancer pain and hyperbilirubinemia. In general, these therapies were shown to be safe and no severe AEs are related to the treatment [Kunii et al, 2009; Motohashi et al, 2009; Uchida et al, 2008; Ishikawa et al, 2005].

The AEs reported in early phase WT1- peptide vaccine clinical studies in AML and MDS patients were mainly grade 1 or 2 events including, fatigue, headache, pruritus, muscular weakness, bone pain, pain in extremity, flushing, dry skin, transient local erythema and induration, fever, transient erythema nodosum-like lesions and persistent cough. Also, grade 3 and 4 AEs reported as lymphocyte count decrease, neutrophil count decrease, white blood cell count decrease and platelet count decrease. Overall, the protocol treatments were well tolerated and associated only with transient local grade 1 or 2 toxicities [Maslak, 2018; Keilholz et al, 2009].

In addition, based on the above and the mechanism of action of ASP7517, immune-related adverse reactions (e.g., fever, headache, fatigue, hot flashes, diarrhea and muscular and joint pain) should be considered and managed as required per standard of care. In addition, the study medical monitor should be contacted to discuss event monitoring, follow up and study treatment management.

2.3.1.9 Pembrolizumab Risk Assessment

Refer to pembrolizumab package insert, summary of product characteristics monograph or local prescribing information for key safety information and potential toxicities.

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in [Section 10.8 Appendix 8: Infusion Reaction Dose Modification and Treatment (Guidelines for ASP7517 and Pembrolizumab); Section 10.9 Appendix 9: Monitoring of Pembrolizumab Potential Immune-related Adverse Events; Section 10.10 Appendix 10: Dose Modification and Toxicity Management for Immune-related AEs; and Section 10.11 Appendix 11 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab].

Note: There is a potential for an increase of rate and/or frequency on immune-related adverse events (irAEs) due to the overlap of immune therapy.

2.3.2 Risk Mitigation

The study population is restricted to participants with advanced/metastatic solid tumors who have received, declined or had a contraindication to all therapy with established clinical benefit for their malignancy. Strict adherence to the eligibility criteria is essential to ensure investigators select appropriate participants for participation in the study.

Additionally, the following precautions mitigate risk and protect participant safety:

- Conservative criteria for interruption and/or discontinuation of study treatment.
- The Dose Escalation and Safety Committee (DESC) will convene once a dose level cohort completes the dose limiting toxicity (DLT) observation period and the data are available for review. The committee's decision on the dose level for the next cohort will be guided according to the Bayesian optimal interval (BOIN) Design based on DLTs observed in the DLT observation period. While safety data from the DLT observation period in the escalation cohorts are the minimum safety data needed for the committee meeting, all available safety findings, including those occurring after the designated DLT observation period that meet DLT criteria ("delayed DLT"), will be considered by the committee.
- The safety in the expansion cohorts will be monitored using Bayesian logistic model and based on all DLT data obtained up to that time from both escalation cohorts and expansion cohorts and drug-related treatment-emergent adverse events (TEAEs) leading to death. Safety monitoring with these models will be started when an expansion cohort is opened. Enrollment in expansion cohorts may be held based on the criteria described in Section 9.5.

The potential risk of irAEs and infusion-related reactions (IRRs) may be mitigated by closely monitoring participants' symptoms, signs and clinical laboratory test results to facilitate early identification and management, as per the guidelines in Section 10.8 Appendix 8: Infusion Reaction Dose Modification and Treatment (Guidelines for ASP7517 and Pembrolizumab); Section 10.9 Appendix 9: Monitoring of Pembrolizumab Potential Immune-related Adverse Events; Section 10.10 Appendix 10: Dose Modification and Toxicity Management for

Immune-related AEs; and Section 10.11 Appendix 11: Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab]. The management of such toxicities should be based on institutional standard of care and published guidelines, as appropriate based on investigator judgment, and on the protocol instructions regarding interruption or discontinuation of study drug treatment.

2.3.3 Benefit Assessment

ASP7517 has effects against WT1 expressing tumors by stimulating innate and adaptive immunity and showed no significant safety findings in the preclinical pharmacology studies. In the repeated dose toxicity studies with mice, all major findings were reversible and monitorable; therefore, ASP7517 may provide benefit of effective and safe treatment in solid tumors with limited treatment option upon progression.

Pembrolizumab is a humanized monoclonal antibody that targets programmed cell death protein 1 (PD-1) receptors on T lymphocytes targeting the negative regulators of the immune response rather than the tumor itself; thus, these agents are not specific to any type of malignancy therefore it has shown antitumor activity in various tumor types. Pembrolizumab has been approved to treat metastatic melanoma, non-small cell lung cancer and any unresectable or metastatic solid tumor with microsatellite instability and DNA mismatch repair deficiency. Pembrolizumab may improve the effect of ASP7517 since the inhibition of the binding of PD-1 to its ligands prevents immune evasion by cancer cells. As such, pembrolizumab would prime the immune system and make cancer cells more susceptible to the immune system which can be activated by ASP7517.

Animal models suggest that ASP7517 treatment combinations with PD-1 pathway blockade may provide additive antitumor effect.

The majority of patients treated with the current standard of care including with anti-PD-1 monotherapies do not achieve objective responses, and most tumor regressions are partial rather than complete. The majority of patients with metastatic disease are not cured with available therapies, underscoring the urgent need for new therapies that will improve the clinical outcomes of these patients.

2.3.4 Overall Risk-Benefit Conclusion

ASP7517 has effects against WT1 expressing tumors and showed no significant safety findings in the preclinical pharmacology studies. In the mice repeated dose toxicity studies of ASP7517, all major findings were reversible and monitorable and will not interfere with human clinical studies considering its potential benefit against the risk.

Despite their clinical benefit, checkpoint inhibitors (CPIs) have side effects that are unique compared to traditional chemotherapy. The immune related side effects associated with CPIs can manifest in a number of organ systems, including gastrointestinal, endocrine, hepatic, and skin. With combination therapy of different CPIs, the toxicities are expected to overlap.

Overall, the risk associated with participation in this clinical study of ASP7517 as single agent and in combination with pembrolizumab is considered to be acceptable for this

population of participants with advanced/metastatic solid tumors who have received, declined or had a contraindication to all therapy with established clinical benefit for their malignancy (except the CPI-naïve melanoma cohort in phase 2).

In addition, the adequate study design with the strict adherence to the eligibility criteria, safety assessments, dosing and stopping/discontinuation rules is essential and will ensure participant safety on the study.

3 OBJECTIVES, ENDPOINTS

Table 8 Study Objectives and Endpoints

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
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)
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

Table continued on next page

Objectives	Endpoints
Exploratory *(continued)*	
● 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., IFNγ 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; IFNγ: 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.

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Overall Study Design

This study is a phase 1/2, open-label study of ASP7517 as monotherapy and in combination with pembrolizumab in selected participants 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). Japan sites will participate only in the phase 2 monotherapy arm.

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

4.1.1 Study Periods

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 up to 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 96 weeks and may receive pembrolizumab monotherapy up to a total of 17 doses every 6 weeks for qualifying participants).
- Survival Follow-up: Telephone contact will be made every 3 months for up to 12 months.

4.1.2 ASP7517 Monotherapy Arm in Dose Escalation Phase 1 Cohort

For ASP7517 Monotherapy Arm in Dose Escalation portion participants will receive 1 dose of ASP7517 on Day 1 of each 28-day cycle for up to 6 doses. Following the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as radiological response or stable disease [SD], or reduction of disease-related symptoms) may continue further treatment with ASP7517, as decided by the investigator.

Participants who achieve confirmed complete response (CR) within the first 4 cycles will not receive further treatment with ASP7517, and participants who achieve partial response (PR) or SD after 4 doses may receive an additional 2 doses. An EOT visit will be conducted for all participants within 7 days of EOT determination or prior to the initiation of new anticancer therapy, whichever occurs first.

The starting dose level is 1×10^7 cells/dose and the decision to escalate to the next dose level (1×10^8 cells/dose) will be made based on the assessment of safety variables, including the occurrence of dose limiting toxicities (DLTs). Dose level may be de-escalated to a lower dose level (1×10^6 cells/dose) based on the occurrence of DLTs.

After the EOT visit, participants will complete 30-day, 60-day and 90-day safety follow-up visits from the last dose of ASP7517 or prior to the initiation of new anticancer therapy.

All participants will enter an observation period except those with confirmed disease progression by immune response evaluation criteria in solid tumors (iRECIST) (iCPD), unconfirmed disease progression based on iRECIST (iUPD) (per independent central review or local review) and who are not clinically stable or clinical progression is confirmed by the investigator. Participants in the Monotherapy Arm Observation Period will be followed for up to 48 weeks starting at EOT until iCPD per independent central review, initiation of a new

anticancer therapy or meeting 1 of the Observation Period discontinuation criteria, whichever occurs first. Safety Follow-up period is included in Observation Period.

All participants will be followed for survival, subsequent anticancer treatments and treatment outcomes following the conclusion of the Observation Period.

Refer to [Section 4.1.5] for additional dose escalation cohort management details.

4.1.3 ASP7517 and Pembrolizumab Combination Therapy Arm in Dose Escalation Phase 1 Cohort

In the combination treatment arm, ASP7517 will be given on Day 1 of each 28-day cycle for up to 6 doses in combination with pembrolizumab for up to 4 doses administered every 6 weeks, starting from Day 1 of Cycle 1. For combination treatment, a 400 mg pembrolizumab infusion will be administered first, followed by an ASP7517 infusion at least 1 hour after the completion of the pembrolizumab infusion. Following the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as radiological response or SD, or reduction of disease-related symptoms) will continue further treatment with ASP7517 and pembrolizumab as decided by the investigator. Participants who achieve confirmed CR within the first 4 cycles will not receive further treatment with ASP7517 at Cycle 5 and Cycle 6 (end of Treatment period) and participants who achieve PR or SD after 4 doses may receive additional 2 doses of ASP7517 in combination with pembrolizumab.

Participants completing the Treatment period who enter the Observation Period with CR, PR or SD are allowed to continue on pembrolizumab alone up to a total of 17 doses for those participants who, in the opinion of the investigator, are continuing to derive clinical benefit.

Subsequent to the Treatment period, all participants, except those with iCPD, iUPD who are not clinically stable or have clinical disease progression per independent central review or local review will enter the Observation Period to monitor treatment response. Participants in the Combination Arm Observation Period will be followed for up to 78 weeks starting at EOT until iCPD (confirmed by independent central review or local review), initiation of a new anticancer therapy or meeting 1 of the Observation Period discontinuation criteria, whichever occurs first. If participant discontinues combination treatment of ASP7517 at any time prior to C5D15, then the participant should continue observation period up to a total of 96 weeks.

After discontinuation of IP, all participants will complete an EOT visit, along with 30-, 60- and 90-day safety follow-up visits from the last dose of IP or prior to the initiation of new anticancer treatment.

The initial dose escalation cohort of pembrolizumab combination with ASP7517 will use a starting dose of ASP7517 1×10^7 cells/dose.

The decision to escalate to the next dose level (1×10^8 cells/dose) will be made based on the assessment of safety variables, including the occurrence of DLTs. A dose level of ASP7517 may be de-escalated to a lower dose level (1×10^6 cells/dose) based on the occurrence of

DLTs. Refer to [Section 10.1.5.1 Dose Escalation and Safety Committee] for details about the DESC.

All participants will be followed for survival, subsequent anticancer treatments and treatment outcomes following the conclusion of the Observation Period.

4.1.4 Dose Limiting Toxicity Criteria

A DLT is defined as any of the following 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), version 5.0.

4.1.4.1 ASP7517 Monotherapy Arm DLTs

- Non-hematologic AEs that are ≥ grade 3 and that do not resolve to ≤ grade 2 within 72 hours of onset
- Confirmed Hy's law case
- IRR that requires the infusion to be discontinued
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1
- Grade ≥ 3 thrombocytopenia accompanied by bleeding that requires transfusion or hospitalization
- Grade ≥ 3 anemia requiring transfusion
- Grade 3 febrile neutropenia with or without infection
- Grade 5 treatment-related toxicity

The following AEs will not be considered as DLTs in the ASP7517 monotherapy arm:

- Electrolyte abnormalities that are not associated with clinical sequelae or deemed not clinically significant and corrected with appropriate management or supplementation within 72 hours of onset
- Grade 3 infusion site reaction if successfully managed and resolved within 72 hours
- Alopecia, anorexia or fatigue
- Grade 3 nausea and/or vomiting if not requiring tube feeding or total parenteral nutrition, or diarrhea and/or constipation if not requiring or prolonging hospitalization that can be managed to grade ≤ 2 with standard antiemetic or antidiarrheal medications used at prescribed dose within 72 hours of onset
- Grade 3 liver function test (LFT) elevations that resolve to ≤ grade 1 within 7 days; LFT elevations lasting > 7 days that are considered to be clinically significant and at least possibly related to ASP7517 will be considered to be a DLT
- Grade 3 irAEs that resolve to ≤ grade 1 within 72 hours of onset

4.1.4.2 ASP7517 and Pembrolizumab Combination Therapy Arm DLTs

- Grade ≥ 3 non-hematological AE that does not resolve to ≤ grade 2 within 72 hours of onset

- Grade ≥ 3 febrile neutropenia
    - Grade 3 febrile neutropenia is defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour.
    - Grade 4 febrile neutropenia is defined as ANC < 1000/mm^3 with a single temperature of > 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Grade ≥ 3 thrombocytopenia accompanied by bleeding that requires transfusion or hospitalization
- Grade ≥ 3 anemia requiring transfusion
- Grade ≥ 2 pneumonitis
- Grade ≥ 2 encephalopathy, meningitis or motor or sensory neuropathy
- Confirmed Hy's law cases
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN) in participants without liver metastases
- AST or ALT > 8 × ULN in participants with liver metastases
- Total bilirubin (TBL) > 3 × ULN (grade ≥ 3)
- Guillain-Barré syndrome or myasthenic syndrome/myasthenia gravis
- IRR that requires the infusion to be discontinued
- Prolonged delay (> 2 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1
- Grade 5 treatment-related toxicity

Participants experiencing a DLT will be discontinued from the study unless the participants are deriving clinical benefit from the study treatment in the opinion of the investigator; in those cases, after discussion with the sponsor, participants may be allowed to continue study treatment with ASP7517 upon resolution of the DLT event to ≤ grade 1 or baseline. 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.

DLTs Requiring Discontinuation of Treatment

- If a study participant develops a grade 4 DLT after receiving Cycle 1, then the study participant should not receive Cycle 2 of the study product.
- If a study participant develops a grade ≥ 3 non-hematological AE that does not resolve to ≤ grade 2 within 72 hours of onset, it should be considered a DLT and the study participant should not receive Cycle 2 of the study product.

If there is a delay in administration of Cycle 2 by > 4 weeks, it may result in discontinuation of Cycle 2 after discussion with the sponsor.

4.1.5 Phase 1 Dose Escalation

4.1.5.1 Safety Requirement for Monotherapy and Combination Therapy Dose Escalation

After dosing with ASP7517, participants must be observed for safety for a minimum of 4 hours in the dose escalation phase. The safety observation will consist of hourly AE observations. If new AEs are observed that are ≥ grade 3 during this time, participants should continue to be observed at the investigator's discretion. The participant should be followed on an outpatient basis on planned visits during the DLT assessment period to closely monitor any AEs.

The following vital sign assessment schedules apply:

- At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, vital signs are obtained predose (-1 h from start of pembrolizumab infusion), within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion, at the end of the pembrolizumab infusion (-5 to +10 min window), 30 min (± 10 min) after completion of the pembrolizumab infusion, within 15 min prior to the start of the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to +10 min window), and postdose (+30 min, +1, +2, +3 and +4 h [± 10 min window each] from end of the ASP7517 infusion).
- ASP7517 dosing only: Vital signs will be obtained within 15 min prior to start of the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to + 10 min window), as well as 30 min (± 5 min), 1 h (± 10 min) and 2 h (± 10 min) after completion of the ASP7517 infusion. If participants are still available, additional optional vital sign assessments 3 h (± 10 min) and 4 h (± 10 min) after completion of the ASP7517 infusion will be obtained.
- Pembrolizumab dosing only: Vital signs will be obtained within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion (-5 to + 10 min window), at the end of the pembrolizumab infusion (-5 to + 10 min window) and at 30 min (± 10 min) after completion of the pembrolizumab infusion for participants in the combination therapy.

4.1.5.2 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 DLT-evaluable participants.

Dose escalation will be guided according to the BOIN design [Liu & Yuan, 2015] to determine the next dose level based on DLT occurrence. After the planned number of evaluable participants has completed the DLT observation period for a given dose level, safety for that dose level will be assessed. Each dose level in the dose escalation will enroll

3 to 4 evaluable participants for the initial assessment of each dose level. Refer to the *Participant Replacement during Dose Escalation Cohort* section for definition of evaluable participants. If the decision is made to remain at the current dose level, an additional 3 or 4 evaluable participants may be enrolled at the current dose level. Three to 12 participants will be enrolled in the dose escalation cohort. A minimum of 6 participants must be enrolled at the dose level used to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) of ASP7517.

Study enrollment and study treatment will be temporarily interrupted during dose escalation of monotherapy or combination therapy arms pending review of the following:

- Any death that is not related to disease progression occurring within 30 days of receiving IP
- Occurrence of 2 grade ≥ 4 DLTs in 2 study participants
- Any grade 4 hypersensitivity reaction/anaphylaxis

Participant Replacement during Dose Escalation Cohort

Participants may be replaced in the dose escalation cohort if:

- 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 decision regarding replacement of individual participants will be made by the sponsor with discussions with the treating investigator.

Participants who experience DLTs in the dose escalation cohort will not be replaced.

Refer to [Section 10.1.5.1 Dose Escalation and Safety Committee] for details about the DESC.

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.

4.1.6 Phase 2 Dose Expansion Cohort

4.1.6.1 Monotherapy Arm Dose Expansion Cohort

Monotherapy dose expansion will be opened after the phase 1 monotherapy arm dose escalation cohort has been completed and RP2D is established. If a confirmed response (PR based on iRECIST [iPR] or a CR based on iRECIST [iCR], per independent central review) is observed in a monotherapy arm dose escalation cohort, a tumor-specific dose expansion cohort may be opened in that tumor type after the phase 1 dose escalation has been completed. Once RP2D is determined; the melanoma expansion cohort may be opened (even if no response is observed in the 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.

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. Initially, 18 participants will be enrolled in a tumor-specific expansion cohort at each designated dose level (stage 1). If the iORR does not meet the optimal stopping boundaries (see table below), then an additional 25 participants will be enrolled for a total maximum sample size of 43 for that tumor type at each dose level (stage 2). Otherwise, the enrollment at that dose level will be closed. When the total number of participants reaches the maximum sample size of 43, it may be predicted that ASP7517 is efficacious if the number of responses is greater than or equal to 8.

Optimized Stopping Boundaries for Monotherapy Arm	
Number of participants treated	**Stop if number of responses ≤**
18	2

If more than 1 dose level is open for enrollment within a selected tumor type, the newly enrolled participants with that tumor type will be randomly allocated to one of the open dose levels. Randomization will be weighted toward 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, the next participant would be randomly allocated to dose level ‘x’ or ‘y’ with the ratio of 15:18.

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

When escalation and expansion cohorts are both open for enrollment, enrollment into escalation cohorts takes priority such that participants who are eligible for both will be

preferentially enrolled in the escalation cohorts. Additionally, enrollment in the expansion cohorts may be prematurely closed at the discretion of the sponsor.

4.1.6.2 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 and MTD/RP2D of ASP7517 combination therapy has been determined. The metastatic melanoma CPI naïve cohort will be opened first. 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.

For metastatic melanoma CPI naïve participants, initially 20 participants will be enrolled in an expansion cohort at each designated dose level (stage 1). If the iORR per independent central review does not meet the optimal stopping boundaries (see table below) for metastatic melanoma CPI naïve participants, then an additional 49 participants will be enrolled for a total maximum sample size of 69 at each dose level. When the total number of participants reaches the maximum sample size of 69, it may be predicted that the combination therapy with ASP7517 and pembrolizumab arm is effective if the number of responses is greater than or equal to 24.

Optimized Stopping Boundaries for Metastatic Melanoma (CPI Naïve) Combination Therapy Arm	
Number of participants treated	**Stop if number of responses ≤**
20	4

CPI: checkpoint inhibitor

For ovarian cancer, initially 19 participants will be enrolled in an expansion cohort at each designated dose level (stage 1). If the iORR per independent central review does not meet the optimal stopping boundaries (see table below) for ovarian cancer, then an additional 36 participants will be enrolled for a total maximum sample size of 55 at each dose level. When the total number of participants reaches the maximum sample size of 55, it may be predicted that the combination therapy with ASP7517 arm is effective if the number of responses is greater than or equal to 13.

Optimized Stopping Boundaries for Ovarian Cancer Combination Therapy Arm	
Number of participants treated	**Stop if number of responses ≤**
19	3

For CRC, initially 21 participants will be enrolled in an expansion cohort at each designated dose level (stage 1). If the iORR per independent central review does not meet the optimal stopping boundaries (see table below) for CRC, then an additional 39 participants will be enrolled for a total maximum sample size of 60 at each dose level. When the total number of

participants reaches the maximum sample size of 60, it may be predicted that the combination therapy with ASP7517 arm is effective if the number of responses is greater than or equal to 16.

Optimized Stopping Boundaries for Colorectal Cancer Combination Therapy Arm	
Number of participants treated	**Stop if number of responses ≤**
21	4

For metastatic melanoma CPI refractory participants, initially 20 participants will be enrolled in an expansion cohort at each designated dose level (stage 1). If the iORR per independent central review does not meet the optimal stopping boundaries (see table below) for metastatic melanoma CPI refractory participants, then an additional 28 participants will be enrolled for a total maximum sample size of 48 at each dose level. When the total number of participants reaches the maximum sample size of 48, it may be predicted that the combination therapy with ASP7517 arm is effective if the number of responses is greater than or equal to 11.

Optimized Stopping Boundaries for Metastatic Melanoma (CPI Refractory) Combination Therapy Arm	
Number of participants treated	**Stop if number of responses ≤**
20	2

CPI: checkpoint inhibitor

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.

UNIQUE to Japan Sites

Japanese participants will be enrolled in the monotherapy arm of the dose expansion cohort.

4.2 Scientific Rationale for Study Design

This study was designed to evaluate ASP7517 as monotherapy and in combination with pembrolizumab in selected participants with advanced solid tumors known to express WT1 antigen. Antitumor efficacy of ASP7517 was demonstrated in preclinical AML model in which mice displayed significantly prolonged survival times.

The rationale for evaluating the combination of ASP7517 and pembrolizumab is supported by preclinical in vivo studies obtained from mice models that show superior antitumor activity of combination therapy over monotherapy. Longer survival period was shown by aAVC-WT1 treatment in combination with anti-PD1 antibody relative to aAVC-WT1 alone. The prolonged survival time most likely results from WT1-specific antitumor effect induced

by aAVC (NIH3T3)-WT1. This suggests additive activity of ASP7517 with CPIs like pembrolizumab, which are known to restore immune system tumor surveillance, while ASP7517 functions by stimulating the immune system. Therefore, combination therapy may lead to higher rates of response in cancer patients compared to monotherapy. However, the combination may also increase the frequency or severity of toxicities, and thus, a dose escalation study is the appropriate setting to explore this combination.

In this study, each participant will receive ASP7517 as monotherapy or in combination with pembrolizumab every 28 days.

The design will closely monitor safety while efficiently assessing efficacy of ASP7517 dose levels of 1×10^7 cells/dose and 1×10^8 cells/dose as monotherapy and in combination with pembrolizumab fixed dose of 400 mg every 6 weeks.

Tumor-specific expansion cohorts may be triggered by a confirmed response to ASP7517 or to the combination with pembrolizumab, or following the determination of RP2D. The types of cancer selected for the expansion cohorts were based on expression of WT1 in the tumor. Expansion will be initiated in melanoma (CPI naïve in the combination arm and CPI refractory in the monotherapy arm). A gated design in the expansion phase is being implemented to allow expansion into CRC and ovarian cancer. This gated design will allow early evaluation of response, avoiding a large number of participants being exposed to ineffective treatment. If antitumor activity is observed in dose escalation or melanoma dose expansion Stage 1, expansion cohorts for CRC and ovarian cancer may be opened.

In the expansion phase of the combination arm, participants with metastatic melanoma are excluded if they received prior treatment with CPI. This will establish the efficacy of the combination of ASP7517 with pembrolizumab in CPI naïve participants. Also, there is no eligibility selection criteria for PD1 expression since it is not required per the pembrolizumab package insert for the tumor selected for the expansion phase.

In addition, participants with HIV will be excluded since the compromised immune system may affect the immune response of ASP7517.

Objective response rate (ORR) is selected as a suitable efficacy primary endpoint in such an early phase study because it can generally be assessed early and with a smaller sample size compared with survival studies. In addition, it provides an informative presentation of effect on tumor attributable to treatment since it is based on objective and quantitative assessment.

Based on the above, this study is designed appropriately to assess safety and efficacy of ASP7517 as monotherapy and in combination with pembrolizumab in the selected participants.

4.3 Dose Rationale

4.3.1 ASP7517

Nonclinical pharmacology data suggest ASP7517-surrogate shows prolonged survival when administered intravenously to the C1498-WT1 inoculated mouse AML model (per 30 g mouse), and prolonged survival was confirmed at the lowest dose level (5×10^2 cells/mouse)

in the study. The dose of 5×10^2 cells/mouse is calculated as 1.7×10^4 cells/kg (5×10^2 cells/30 g); therefore, the starting dose is estimated to be 1×10^6 cells/dose (1.7×10^4 cells/kg $\times$ 60 kg) for the first-in-human 7517-CL-0101 study, since the toxicology profile observed in the nonclinical studies was considered to be acceptable to initiate a clinical study at this dose level. In study 7517-CL-0101, 1×10^6 cells/dose and 1×10^7 cells/dose were completed with no DLT and determined to be safe by DESC. To date, 7 participants completed the DLT observation phase in the 1×10^8 cells/dose cohort without experiencing any DLTs, and DESC determined this dose level to be tolerable. Currently, additional participants are being enrolled in the 1×10^8 cells/dose cohort to confirm safety and tolerability. The starting dose of ASP7517 for study 7517-CL-1101 is selected to be 1×10^7 cells/dose for both monotherapy and combination therapy arms to balance protection of participant safety with efficient dose escalation.

The dosing regimen of ASP7517 for this study will be treatments on Day 1 of each 28-day cycle, which is supported by nonclinical pharmacology and toxicology data. In mice immunized with specific antigen expressing aAVC at Day 0 and Day 28, NKT cells and T cells were stimulated after each administration, and recovery of toxicities were confirmed upon 28-day interval. Multiple administrations up to 6 doses are selected due to the immunosuppressive tumor microenvironment requiring repeated immune system reactivation to achieve response.

4.3.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 400 mg every 6 weeks. Recently, the manufacturer of pembrolizumab (Merck) has gained regulatory approval for a more convenient dosage in adults across all indications and regardless of tumor: 400 mg every 6 weeks based on additional pharmacokinetic simulations [KEYTRUDA prescribing information, June 2020]. This schedule has demonstrated to provide equivalent exposure to the approved dosage of 200 mg every 3 weeks [Lala et al, 2018; Goldstein et al, 2017]

The pharmacokinetic simulations study demonstrated that a dosage of 400 mg every 6 weeks provides adequate trough target engagement even for participants whose weights are higher than average, with occupancy of 97% for participants weighing 100 kg and 96% for those weighing 150 kg [Canadian Agency for Drugs and Technologies in Health, CADTH technology review, 2019].

4.4 End of Study Definition

The study start is defined as the date the first participant signs the informed consent form (ICF). End of study is defined as the last visit or scheduled procedure shown in the schedule of assessments for the last participant in the study.

Study completion is defined as the conclusion of data collection for the defined study endpoints. The study may be closed within a participating country per local regulations once the study has been completed and if all participants enrolled in the country are no longer receiving IP.

5 STUDY POPULATION

All screening assessments must be completed and reviewed to confirm the potential participant meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

5.1 Inclusion Criteria

Participant is eligible for participation in the study if all of the following apply:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations (e.g., HIPAA Authorization for U.S. sites) must be obtained from the participant prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. The participant is at least 18 years of age and legally an adult according to local regulation at the time of signing informed consent.
3. Participant has locally-advanced (unresectable) or metastatic solid tumor malignancy that is confirmed by available pathology records or current biopsy. Participant must also have received all standard therapies (unless the therapy is contraindicated or intolerable) appropriate to provide clinical benefit in the opinion of the treating investigator for his/her specific tumor type. However, participants with metastatic melanoma who have not received CPIs (i.e., CPIs naive) may enroll in the phase 2 Combination Therapy Arm Dose Expansion Cohort to receive CPI: Pembrolizumab.
4. Participant must be diagnosed with solid tumor known to express WT1 antigen such as, but not limited to melanoma, ovarian cancer or CRC (Examples of WT1 expressing cancers, please see literature reference by Sugiyama [2010]).
5. Participant consents to provide an archival tumor specimen in a tissue block or unstained serial slides, if available, prior to study treatment.
6. Participant has an Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.
7. Participant's last dose of prior antineoplastic therapy, including any immunotherapy, was 21 days or 5 half-lives, whichever is shorter, prior to initiation of IP administration. A participant with BRAF gene, epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutation positive non-small cell lung carcinoma is allowed to remain on EGFR tyrosine kinase inhibitor (TKI) or ALK or BRAF inhibitor therapy until 4 days prior to the start of IP administration.
8. Participant has completed any radiotherapy (including stereotactic radiosurgery) at least 2 weeks prior to IP administration.
9. Participant's AEs (excluding alopecia) from prior therapy have improved to grade 1 or baseline within 14 days prior to start of IP.
10. Participant has adequate organ function prior to start of IP as indicated by the following laboratory values. If a participant has received a recent blood transfusion, the laboratory tests must be obtained ≥ 4 weeks after any blood transfusion:

Parameter	Laboratory Value
Hematological	
ANC	≥ 1500/µL
Platelets	≥ 100000/µL
Hemoglobin	≥ 9 g/dL
Renal	
Creatinine	Either: a) ≤ institutional ULN, OR b) Estimated glomerular filtration rate* (eGFR) ≥ 45 mL/min/1.73m^2 if creatinine is > ULN *Using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (2009); online calculator: https://www kidney.org/professionals/kdoqi/gfr_calculator
Total bilirubin	Either: a) ≤ 1.5 × ULN; or b) Direct bilirubin ≤ ULN **and** total bilirubin < 3 × ULN (for participants with Gilbert's syndrome)
AST (SGOT) and ALT (SGPT)	≤ 2.5 × ULN

ALT: alanine aminotransferase; ANC: absolute neutrophil count, AST: aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; ULN: upper limit of normal

11. A female participant is eligible to participate if she is not pregnant (see [Section 10.2 Appendix 2: Contraception Requirements]) and at least 1 of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP) (see [Section 10.2 Appendix 2: Contraception Requirements])

       OR

    b. WOCBP who agrees to follow the contraceptive guidance (see [Section 10.2 Appendix 2: Contraception Requirements]) from the time of informed consent through at least 6 months after the final IP administration.
12. Female participant must agree not to breastfeed starting at screening and throughout the IP and for 180 days after the final IP administration.
13. Female participant must not donate ova starting at screening and throughout the IP and for 180 days after the final IP administration.
14. A male participant with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception (see [Section 10.2 Appendix 2 Contraception Requirements]) throughout the treatment period and for at least 180 days after the final IP administration.
15. Male participant must not donate sperm during the treatment period and for 180 days after the final IP administration.
16. Male participant with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 180 days after the final IP administration.
17. Participant agrees not to participate in another interventional study while receiving IP.

Additional Inclusion Criteria for Participants in the Expansion Cohorts:

1. Participant meets one of the following:
   - Participant has the tumor type for which a confirmed response was observed in a monotherapy dose escalation cohort (monotherapy arm only) cohort; OR
   - For tumor specific expansion cohorts of ASP7517 or ASP7517 with pembrolizumab, participant has the applicable tumor type; CPI refractory metastatic melanoma (monotherapy and combination arms), CPI naïve melanoma (combination arm only), ovarian cancer, CRC.
2. Participant has at least 1 measurable lesion per response evaluation criteria in solid tumors (RECIST) v1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
3. Participant consents to provide a tumor specimen in a tissue block or unstained serial slides obtained within 56 days prior to first dose of IP. If a recent tissue sample cannot be provided due to medical or safety concerns, enrollment into the study must be discussed with the medical monitor.
4. Participant consents to undergoing a tumor biopsy (core tissue biopsy or excision) during the treatment period as indicated in the schedule of assessments if predose biopsy is available and if medically feasible.

Waivers to the inclusion criteria will **NOT** be allowed.

5.2 Exclusion Criteria

Participant will be excluded from participation in the study if any of the following apply:

1. Participant weighs < 45 kg at screening.
2. Participant has received investigational therapy (other than an investigational EGFR TKI in a participant with EGFR activating mutations or ALK or BRAF inhibitor in a participant with an ALK mutation) within 21 days or 5 half-lives, whichever is shorter, prior to start of IP.
3. Participant requires or has received systemic steroid therapy or any other immunosuppressive therapy within 14 days prior to C1D1. Participants using a physiologic replacement dose of hydrocortisone or its equivalent (defined as up to 30 mg per day of hydrocortisone up to 10 mg per day of prednisone) are allowed.
4. Participant has symptomatic central nervous system (CNS) metastases or participant has evidence of unstable CNS metastases even if asymptomatic (e.g., progression on scans). Participants with previously treated CNS metastases are eligible, if they are clinically stable and have no evidence of CNS progression by imaging for at least 4 weeks prior to start of IP and are not requiring immunosuppressive doses of systemic steroids (> 30 mg per day of hydrocortisone or > 10 mg per day of prednisone or equivalent) for longer than 2 weeks.
5. Participant has an active autoimmune disease. Participants with type 1 diabetes mellitus, endocrinopathies stably maintained on appropriate replacement therapy or skin disorders (e.g., vitiligo, psoriasis or alopecia) not requiring systemic treatment are allowed.

6. Participant was discontinued from prior immunomodulatory therapy due to a grade ≥ 3 toxicity that was mechanistically related (e.g., immune related) to the agent in the judgment of the investigator.
7. Participant has known history of serious hypersensitivity reaction to a known ingredient of ASP7517 or pembrolizumab or severe hypersensitivity reaction to treatment with another monoclonal antibody.
8. Participant has a known history of human immunodeficiency virus.
9. Participant with known history of positive hepatitis B surface antigen or isolated hepatitis B core antibody (including acute HBV or chronic HBV) or hepatitis C ([HCV] ribonucleic acid [RNA] detected by qualitative assay). Hepatitis C RNA testing is not required in participants with negative hepatitis C antibody testing.
10. Participant has received a live vaccine against infectious diseases within 28 days prior to initiation of IP.
11. Participant has a history of drug-induced pneumonitis (interstitial lung disease), a history of (non-infectious) pneumonitis that required steroids, radiation pneumonitis or currently has pneumonitis.
12. Participant has an infection requiring systemic therapy within 14 days prior to IP.
13. Participant has received a prior allogeneic bone marrow or solid organ transplant.
14. Participant is expected to require another form of antineoplastic therapy while on IP.
15. Participant has had a myocardial infarction or unstable angina within 6 months prior to the start of IP or currently has an uncontrolled illness including, but not limited to symptomatic congestive heart failure, clinically significant cardiac disease, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
16. Participant has a clinically significant abnormal electrocardiogram at screening in the investigator's opinion.
17. Participant has symptomatic cardiovascular disease within the preceding 12 months unless cardiology consultation and clearance has been obtained for study participation, including but not limited to the following: significant coronary artery disease (e.g., requiring angioplasty or stenting), acute myocardial infarction or unstable angina pectoris < 3 months prior screening, uncontrolled hypertension, clinically significant arrhythmia or congestive heart failure (New York Heart Association grade ≥ 3).
18. Any condition that, in the investigator's opinion, makes the participant unsuitable for study participation.
19. Participant has had a major surgical procedure and has not completely recovered within 28 days prior to the start of IP.
20. Participant has a prior malignancy active (i.e., requiring treatment of intervention) within the previous 2 years prior to the screening visit, except for locally curable malignancies that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast. Participants with organ confined prostate cancer with no evidence of recurrent or progressive disease are eligible if hormonal therapy has been initiated or the malignancy has been surgically removed or treated with definitive radiotherapy.

21. Participant has International Normalized Ratio (INR) > 1.5 × ULN and/or activated partial thromboplastin time (aPTT) > 1.5 × institutional normal limits.

Additional Exclusion Criteria for Participants in Combination Expansion Cohorts:

1. Participants with metastatic CRC with documented microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient who have received prior treatment with PD-1 or programmed death-ligand (PD-L1) inhibitors such as nivolumab or pembrolizumab.
2. For CPI naïve metastatic melanoma participants who have received to PD-1 or PD-L1 inhibitors, such as nivolumab or pembrolizumab.
3. Participant with metastatic ovarian cancer with documented MSI-H or MMR deficient who have received PD-1or PD-L1 inhibitors, such as nivolumab or pembrolizumab.

Waivers to the exclusion criteria will **NOT** be allowed.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

A screen failure is defined as a potential participant who signed the ICF, but did not meet one or more criteria required for participation in the study and was not enrolled.

For screen failures, the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the electronic case report form (eCRF).

5.4.1 Rescreening

Results of screening assessments that do not meet the parameters required by eligibility criteria (e.g., clinical laboratory tests, vital signs, physical examination, electrocardiogram [ECG], etc.) may be repeated once within the 28-day screening period without the need to register the participant as a screen failure. If the participant meets exclusion criteria that cannot resolve during the screening period, or more than 28 days elapse from the date of signing the ICF, the participant must be documented as a screen failure. In order to re-screen after prior screen failure, a new ICF must be signed and the participant entered into screening with a new participant identification number. Rescreening is only allowed once for an individual participant.

6 INVESTIGATIONAL PRODUCT(S) AND OTHER STUDY TREATMENT(S)

6.1 Investigational Product(s) and Other Study Treatments Administered

Table 9 Investigational Product(s)

Name	**ASP7517**	**Pembrolizumab for Combination Therapy Arm**
Use	Test product	Test product
Dosage Form	Suspension for injection	Solution for injection
Physical Description	Opalescent and white to slightly yellowish-white suspension	Clear to slightly opalescent, colorless to slightly yellow solution
Unit Dose Strength	1 x 10^7 cells/mL	100 mg/vial
Packaging and Labeling	Clear single use vial	Clear single use vial
Route of Administration	Intravenous infusion	Intravenous infusion
Administration Frequency	Administered intravenously every 28 days	Administered intravenously every 6 weeks
IMP or Non-IMP	IMP	IMP
Sourcing	Provided centrally by sponsor	Provided centrally by sponsor unless otherwise designated

IMP: Investigational Medicinal Product

Refer to the pharmacy manual for detailed information regarding preparation, handling and storage of ASP7517.

For pembrolizumab, refer to the prescribing information for detailed information regarding preparation, handling and storage [KEYTRUDA prescribing information, June 2020].

6.1.1 Investigational Product Administration

ASP7517 will be diluted with normal saline to approximately 50 mL and administered by intravenous infusion at 4 to 6 mL/min infusion rate through a dedicated intravenous line.

Pembrolizumab will be administered at a dose of 400 mg via 30-min intravenous infusion every 6 weeks beginning on C1D1. Sites should make every effort to target infusion timing to be as close to 30 min as possible. However, given the variability of infusion pumps from site to site, a window between -5 min and +10 min is permitted (i.e., infusion time is 30 min (-5 min/+10 min). The pembrolizumab infusion should be completed at least 1 hour prior to ASP7517 injection for participants in ASP7517 and pembrolizumab combination therapy arms.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

All IP used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at APGD or sponsor's designee in accordance with APGD or sponsor's designee standard operating procedures (SOPs), current Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation of Technical Requirements for

Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

Each carton and vial will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

Refer to the pharmacy manual for detailed information regarding packaging and labeling of the IP.

6.2.2 Handling, Storage and Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IP received and any discrepancies are reported and resolved before use of the IP.
- Only participants enrolled in the study may receive IP and only authorized study site personnel may supply or administer IP. Only IP with appropriate expiry/retest dating may be dispensed.
- All IP must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions and access must be limited to the investigator and authorized study site personnel.
- The investigator, institution or the head of the medical institution (where applicable) is responsible for accountability, reconciliation and record maintenance (i.e., receipt, reconciliation and final disposition records).
- Further guidance and instruction on final disposition of used and unused IP is provided in the pharmacy manual.

Refer to the pharmacy manual for detailed information regarding handling, storage and accountability of the IP.

6.3 Randomization

This is an open-label study. Participant enrollment and dispensation of IP will be performed via the interactive response technology (IRT) system. Specific IRT procedures will be described in the respective study manual.

6.3.1 Assignment and Allocation

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 A7517 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.

UNIQUE to Japan Sites

Japanese participants will be enrolled in the monotherapy arm of the dose expansion cohort.

6.4 Investigational Product and Other Study Treatment Compliance

Dosing will take place in the clinical unit. The administration of IP will be supervised to ensure treatment compliance. The exact day and time of IP administration will be documented.

6.5 Dose Modification

Dose modifications of ASP7517 are not allowed at the individual participant level without prior consultation with the sponsor's medical monitor. Any participants who do not receive a subsequent dose within the scheduled time window in the schedules of assessments [Table 1 and Table 2] can only resume treatment after discussion with the medical monitor. Any participant experiencing a grade 3 treatment-related AE after receiving a dose of ASP7517 may receive the subsequent scheduled dose of ASP7517 only after the observed grade 3 treatment-related AE has resolved to grade 1; the subsequent dose of ASP7517 may be reduced to a dose level deemed safe by the DESC. Further treatment reduction/withdrawal can be implemented after discussion with the medical monitor, including for any clinically significant AEs affecting vital organs (e.g., cardiac events).

Refer to the appendices and approved pembrolizumab package insert, summary of product characteristics monograph or local product information supplied by the manufacturer for the recommended treatment modifications for pembrolizumab.

6.6 Continued Access to Investigational Product After the End of the Study

ASP7517 will be given up to a maximum of 6 cycles. ASP7517 and pembrolizumab will not be made available after conclusion of the study to participants who are still receiving and benefitting from study treatment in countries where the product does not have marketing approval and is not commercially available, as the treatment with ASP7517 does not have authorization to be administered after the study is complete.

Pembrolizumab will be administrated per the product insert treatment instructions and further treatment beyond the study period is allowed.

6.7 Treatment of Overdose

In the event of suspected ASP7517 overdose, the participant should receive supportive care and monitoring. The medical monitor/expert should be contacted as applicable.

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥ 5 times the indicated dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event of suspected pembrolizumab overdose, refer to the approved package insert, summary of product characteristics or local product information supplied by the manufacturer for the IP.

Refer to [Section 10.3.7 Reporting Procedures for Special Situations] for reporting requirements for suspected overdose or other medication error.

6.8 Concomitant Therapy

The following treatments are prohibited during the study:

- Investigational agents other than ASP7517 and pembrolizumab
- Steroids and other immunosuppressive therapy: The use of immunosuppressive agents and immunosuppressive doses of systemic steroids (> 30 mg per day of hydrocortisone or > 10 mg per day of prednisone or equivalent) are not allowed during IP unless needed to manage AEs related to IP. The use of topical, ocular, intra-articular, intranasal and inhalational corticosteroids (with minimal systemic absorption) is allowed. Physiologic replacement doses of systemic corticosteroids (≤ 30 mg per day of hydrocortisone or ≤ 10 mg per day of prednisone or equivalent) are permitted. Corticosteroids for prophylaxis (e.g., contrast dye allergy) or for brief treatment of conditions not related to IP (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) are also allowed.
- Vaccines: Live vaccines are prohibited while the participant is receiving IP and for 30 days after last dose of IP. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, Bacillus Calmette-Guerin and typhoid vaccine.
- Other anticancer treatment: The use of other anticancer therapy (e.g., chemotherapy, hormonal therapy, immunotherapy, radiotherapy, biological therapy, targeted therapy) is not allowed during IP; however, participants with metastatic castration resistant prostate cancer who do not have orchiectomy should continue androgen deprivation therapy during the study.
- Palliative (limited field) radiation therapy: for bone metastases is allowed. IP should be interrupted during radiation therapy. The use of bisphosphonates and receptor activator of nuclear factor kappa-B ligand inhibitors for bone metastases is allowed if initiated

prior to screening. Surgical treatment of isolated or symptomatic lesions for palliation or curative management is also allowed.

Refer to [Section 10.5 List of Excluded Concomitant Medications] for a detailed list of drug classes and/or specific medications that are prohibited during participation in the study.

7 STUDY PROCEDURES AND ASSESSMENTS

- Study procedures and their timing are summarized in the schedules of assessments [Table 1 through Table 4]. Adherence to the study design requirements, including those specified in the schedule of assessments, is essential and required for study conduct. Prospective protocol waivers or exemptions are not allowed.
- Any change, divergence or departure from the study design or procedures identified in the protocol is considered a protocol deviation. All deviations from the protocol are to be recorded.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., imaging, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the schedule of assessments.

7.1 Efficacy Assessments

Disease response and progression will be evaluated in this study using the RECIST v1.1 and iRECIST criteria as assessed by independent central review and investigator.

Tumor assessments will be performed at screening and at every 8 weeks (± 1 week) from C1D1 until confirmed disease progression by iRECIST (iCPD). Scans will be read on site and also submitted in digital format for independent central review. Procedures for independent imaging central review will be described in a separate imaging charter. The assessment will include tumor measurements for target lesions, non-target lesions, and assessment for any new lesions. An overall assessment will be characterized for time point evaluation.

Computed tomography (CT) or magnetic resonance imaging (MRI) scans are preferred for this study and to ensure comparability, the same technique (CT/MRI) used at screening should be utilized throughout the study. The same method should be employed and assessed by the same individual on each occasion, when possible. Imaging should include chest, abdomen and pelvis as well as any other anatomical region appropriate for the participant's disease.

Imaging should be done every 8 weeks from C1D1 regardless of treatment interruption or delays and through the follow-up period as applicable. Scans performed prior to informed consent as standard of care are acceptable as screening scans if done within 28 days prior to C1D1. If a biopsy of a target lesion is performed, the baseline scan should be repeated, if possible.

Confirmatory scans for CR or PR should be done at least 4 weeks after the date of the scan that CR or PR was first observed. Confirmatory scans for PD must occur at least 4 weeks after the date of the scan that PD was first observed but no longer than 8 weeks.

7.2 Safety Assessments

7.2.1 Laboratory Assessments

- See [Section 10.6 Appendix 6: Clinical Laboratory Assessments] for the list of clinical laboratory tests to be performed and refer to the schedules of assessments [Table 1 through Table 4] for timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator or subinvestigator who is a qualified physician. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

7.2.2 Vital Signs

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed as specified in the schedules of assessments [Table 1 through Table 4].
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 min of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 min rest and will include temperature, systolic and diastolic blood pressure, and pulse.
- The following vital sign assessment schedules apply:
    - At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, vital signs are obtained predose (-1 hour from start of pembrolizumab infusion), within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion, at the end of the pembrolizumab infusion (-5 to +10 min window), 30 min (± 10 min) after completion of the pembrolizumab infusion, within 15 min prior to the start of the ASP7517 infusion, every 15 min (5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to +10 min window), and postdose (+30 min, +1, +2, +3 and +4 hours [± 10 min window each] from end of the ASP7517 infusion).

- ASP7517 dosing only: Vital signs will be obtained within 15 min prior to start of the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to + 10 min window), as well as 30 min (± 5 min), 1 hour (± 10 min) and 2 hours (± 10 min) after completion of the ASP7517 infusion. If participants are still available, additional optional vital sign assessments 3 hours (± 10 min) and 4 hours (± 10 min) after completion of the ASP7517 infusion will be obtained.
- Pembrolizumab dosing only: Vital signs will be obtained within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion (-5 to +10 min window), at the end of the pembrolizumab infusion (-5 to +10 min window) and at 30 min (± 10 min) after completion of the pembrolizumab infusion for participants in the combination therapy.

7.2.3 Physical Examination

The investigator or designee (a physician or licensed practitioner) will perform standard, full physical examinations as specified in the schedules of assessments [Table 1 through Table 4]. Height and body weight will be measured at the screening visit, and the body weight measurement will be repeated at Day 1 of each cycle. Height measurement may be performed at a subsequent visit if it was not done at screening.

7.2.4 Electrocardiogram

A standard 12-lead ECG will be performed at the screening visit for purposes of assessing participant eligibility. ECG can be repeated during the screening period.

For Dose Escalation:

12-lead ECGs will be recorded in triplicate (at least 2 min apart per time point) and transmitted electronically for central reading. ECGs may be repeated once during screening. On IP administration days, ECGs will be obtained:

- At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of ASP7517.
- ASP7517 dosing only: ECGs are obtained predose (-1 h from start of ASP7517 infusion) and 1 to 2 h post dose of ASP7517.
- Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.

For Dose Expansion:

During ASP7517 and pembrolizumab combination therapy, 12-lead ECGs will be recorded in triplicate (at least 2 min apart per time point) and transmitted electronically for central reading. After treatment with ASP7517 has been discontinued, 12-lead ECGs will be recorded as a single assessment (in triplicate if deemed necessary, at least 2 min apart per

time point) and read locally. On IP administration days, ECG will be obtained predose and 1 to 2 hours post dose. ECG may be repeated once during screening.

ECGs will be recorded after the participant has been in a resting, supine position for at least 5 min. Further details of the procedure will be separately specified in the procedural manual.

7.2.5 Imaging

Chest X-ray or CT scan is to be performed at screening. A chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of screening.

7.2.6 ECOG Performance Status

The ECOG Scale [Oken et al, 1982] will be used to assess performance status [Table 10] at time points outlined in the schedules of assessments [Table 1 through Table 4].

Table 10 ECOG Performance Status

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

ECOG: Eastern Cooperative Oncology Group

7.2.7 Order of Assessments

The following order should be followed when more than one assessment is required at a time point with blood sampling for pharmacokinetics/metabolic profiling being collected nearest to the scheduled time point:

- ECG
- Vital signs
- Blood collection

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in [Sections 10.3.1 and 10.3.2], respectively.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study IP or procedures, or that caused the participant to discontinue the IP or procedures and/or study [see Section 10.3

Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in [Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

7.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the schedule of assessments [Table 1 through Table 4] and reported on the eCRF.

All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the schedule of assessments [Table 1 through Table 4] and reported on the eCRF.

If the NCI CTCAE grade/grade of an SAE/AE changes, the event should be relisted on the eCRF with the new NCI CTCAE grade/grade and new onset date.

If the NCI CTCAE grade/grade decreases, the SAE/AE should be relisted on the eCRF with the new NCI CTCAE grade/grade and new onset date. The exception is ongoing predose events that continue post-dose and improve post-dose. Such events should not be re-listed.

If the NCI CTCAE grade/grade of an SAE reduces, the details of the AE should be provided on the SAE worksheet for the medical assessor to be able to assess the course of the event.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in [Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting]. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study IP or study participation, the investigator must promptly notify the sponsor.

7.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

7.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs (and AEs of special interest [as defined in

Section 7.3.6]) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 8.3]). Further information on follow-up procedures is provided in [Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

If after the protocol-defined AE collection period (see [Section 7.3.1 Time Period for Collecting Adverse Event and Serious Adverse Event Information]), an AE progresses to an SAE, or the investigator learns of any (S)AE (SAE or AE) including death, where he/she considers there is reasonable possibility it is related to the IP or study participation, the investigator must promptly notify the sponsor.

7.3.4 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study IP under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study IP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

Under this protocol, the following event(s) will not be considered as an (S)AE:

- Disease progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as (S)AEs. These data will be captured as efficacy assessment data as outlined in [Section 7.1 Efficacy Assessments]. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the IP and the event, it should be reported as an (S)AE. All deaths up to 30 days after the final administration of IP must be reported as an SAE, even if attributed to disease progression.
- Pre-planned and elective hospital/clinical procedures/interventions or procedures for diagnostic, therapeutic, or surgical procedures for a pre-existing condition that did not worsen during the course of the study. For example, admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the preexisting condition such as transfusion for preexisting anemia, leukopenia or

thrombocytopenia will not be reported as an SAE. These procedures are collected per the eCRF's completion guidelines.

7.3.6 Adverse Events of Special Interest

irAEs are considered AEs of special interest. Participants should be evaluated carefully for potential IRRs as described in [Section 2.3.1.6 Infusion-related Reactions]. In the event a participant is diagnosed with an IRR, then it should be reported as an AE using the diagnosis rather than the list of symptoms. Additional information on the AE of IRR will be collected on the AE eCRF.

If the IRR is also classified as serious, they are to be collected via the SAE/Special Situation worksheet and reported within 24 hours as described in [Section 10.3.6 Reporting of Serious Adverse Events].

7.3.7 Special Situations

Certain special situations observed in association with the IP, such as incorrect administration (e.g., wrong dose of IP or background therapy) are reported as protocol deviations and/or may require special reporting, as described below. These special situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a special situation is associated with, or results in, an AE, the AE is to be assessed separately from the special situation and captured as an AE on the eCRF. If the AE meets the definition of an SAE, the SAE is to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] and the details of the associated special situation are to be included in the clinical description on the special situation worksheet or pregnancy reporting form.

The special situations are:

- Pregnancy
- Lactation
- Medication error, overdose and use outside protocol
- Misuse/abuse
- Occupational exposure
- (Suspicion of) Transmission of infectious agent
- Suspected drug-drug interaction

Instructions and procedures for reporting special situations are provided in [Section 10.3.7 Reporting Procedures for Special Situations].

7.4 Pharmacokinetics

Whole blood will be collected to monitor pharmacokinetics of ASP7517 cells via determination of genomic DNA in the cell by a quantitative polymerase chain reaction method for the dose escalation and expansion cohorts. Sampling time points are as shown in the schedule of assessments [Table 6].

Serum concentrations of pembrolizumab will be evaluated in the combination therapy arm as outlined in the schedule of assessments [Table 6].

Refer to the laboratory manual for detailed information regarding sampling, processing, shipping and storage instructions.

7.5 Pharmacodynamics

Samples for exploratory pharmacodynamics and biomarker analyses of APS7517 will be collected according to the schedules of assessments [Table 1 and Table 3].

The samples described in [Sections 7.5.1 Blood Samples, 7.5.2 Tumor Tissue Samples and 7.5.3 Buccal Swab Samples] may be analyzed for other biomarkers including DNA, RNA and protein, to investigate possible associations with mechanisms of resistance or sensitivity to study treatment, dynamic changes associated with study treatment (in terms of dose, safety, tolerability and efficacy, etc.) and method development or validation of diagnostic assays related to ASP7517.

The samples may be stored at the study sponsor's facility or a contract laboratory facility for up to 15 years after study database closure, at which time the samples will be destroyed. The procedures for the collection, handling and shipping of laboratory samples will be specified in a laboratory manual.

Refer to the laboratory manual for detailed information regarding sampling, processing, shipping and storage instructions.

7.5.1 Blood Samples

Blood samples will be used for the analysis of pharmacodynamics changes related to treatment effect and potential biomarkers of response or resistance related to treatment effect as described in [Section 9.4.5.1 Analysis of Exploratory Biomarker(s)]. Examples of these biomarkers include, but are not limited to, anti-WT1 antibodies, cytokine expression and secretion (e.g., IFNγ), WT1-specific T lymphocytes (e.g., cytotoxic T lymphocytes), immune cell populations (e.g., NKT cells, NK cells, etc.), expression levels of WT1 and mutations in genes that may modify treatment effect.

7.5.2 Tumor Tissue Samples

The tumor tissue will be used for biomarker analyses as described in [Section 9.4.5.1 Analysis of Exploratory Biomarkers(s)]. Examples of biomarkers include, but are not limited to, expression of WT1, expression and mutation of genes that may modify treatment effect, tumor mutational burden, changes in the tumor microenvironment and changes in immune related molecules. Examples include, but are not limited to, CD4 T-cells, CD8 T-cells, etc.

Archival tumor tissue sample: All participants are required to submit (if available) an archival tumor tissue sample in the form of a formalin-fixed, paraffin-embedded (FFPE) block or unstained slides will be collected. If unstained slides are submitted, a minimum of 20 slides (4 to 5-microns thick) is necessary.

Baseline tumor tissue sample: Participants in all expansion cohorts are required to consent to provide a tumor tissue sample (both an FFPE block and frozen sample) obtained within 56 days prior to first dose of study treatment. If the participant has both an FFPE block AND frozen tissue specimen taken within 56 days prior to the first dose of study treatment, a new biopsy is not required.

On-treatment tumor tissue sample: Participants in all expansion cohorts are required to consent to provide an on-treatment tumor tissue sample (both an FFPE block and frozen sample). On-treatment tumor tissue sample is to be collected ± 7 days of the C2D15 visit (or unscheduled).

Details on sample collection, labeling, and shipment procedures will be provided in a separate laboratory manual.

7.5.3 Buccal Swab Samples

Buccal swab samples will be used to genotype the human leukocyte antigen (HLA) gene complex. Knowledge of the specific HLA gene complex in each participant may help understand/explain observed differences in efficacy or treatment effect. The buccal swab will be used for biomarker analyses as described in [Section 9.4.5.1 Analysis of Exploratory Biomarker(s)].

7.6 Pharmacogenomics

Pharmacogenomic (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics, toxicity/safety, efficacy and/or disease. A 4 to 6 mL sample of whole blood for possible banked PGx analysis will be collected as indicated in the schedules of assessments [Table 1 and Table 2] Samples will be shipped to a sponsor-designated sample banking contract research organization (CRO).

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

See [Section 10.7 Appendix 7: Pharmacogenomic Analysis with Banked Sample] for further details on the banking procedures.

7.7 Other Assessments

7.7.1 Replication Competent Lentivirus

Blood samples will be collected and used to monitor the presence of replication competent lentivirus. Sampling time points are as shown in the schedule of assessments [Table 5]. If there is a positive result during the first 18 months of assessments, additional follow-up assessments may be required.

7.8 Total Amount of Blood

The total amount of blood for each participant will vary depending on the course of their disease, duration on treatment and local laboratory requirements. At any time during the

study, if any laboratory abnormalities are found for a participant, additional blood may be drawn for safety monitoring.

The maximum amount of blood collected within 24 hours is approximately 112 mL when an optional PGx sample is collected and 108 mL when an optional PGx sample is not collected.

- Dose Escalation Cohorts:
  For monotherapy with ASP7517
  - Approximately 108 mL of blood will be collected during the Cycle 1 with optional PGx sample, and 104 mL without optional PGx sample
  - Approximately 90 mL of blood will be collected during Cycle 2
  - Approximately 74 mL of blood will be collected at Cycle 3
  - Approximately 82 mL of blood will be collected at Cycle 4
  - Approximately 74 mL of blood will be collected at Cycle 5
  - Approximately 74 mL of blood will be collected at Cycle 6
  - Approximately 36 mL of blood will be collected at EOT depending on the local lab.
  - Approximately 104 mL of blood will be collected during the Survival follow-up period
  - Approximately 34 mL of blood will be collected at the visit during the observation period

  For combination therapy with ASP7517 and pembrolizumab
  - Approximately 112 mL of blood will be collected during Cycle 1 with the optional PGx sample, and 108 mL without the optional PGx sample
  - Approximately 94 mL of blood will be collected during Cycle 2
  - Approximately 74 mL of blood will be collected at Cycle 3
  - Approximately 86 mL of blood will be collected at Cycle 4
  - Approximately 78 mL of blood will be collected at Cycle 5
  - Approximately 74 mL of blood will be collected at Cycle 6
  - Approximately 38 mL of blood will be collected at EOT depending on the local lab.
  - Approximately 40 mL of blood will be collected at the visit during the observation period.

- Dose Expansion Cohorts:

  For monotherapy with ASP7517
  - Approximately 104 mL of blood will be collected during the Cycle 1 with optional PGx sample, and 100 mL without optional PGx sample
  - Approximately 84 mL of blood will be collected during Cycle 2
  - Approximately 56 mL of blood will be collected at Cycle 3
  - Approximately 60 mL of blood will be collected at Cycle 4
  - Approximately 56 mL of blood will be collected at Cycle 5
  - Approximately 56 mL of blood will be collected at Cycle 6
  - Approximately 36 mL of blood will be collected at EOT depending upon the local lab

- Approximately 102 mL of blood will be collected during the Survival follow-up period
- Approximately 34 mL of blood will be collected at the visit during the observation period

For combination therapy with ASP7517 and pembrolizumab

- Approximately 108 mL of blood will be collected during Cycle 1 with the optional PGx sample, and 104 mL without the optional PGx sample
- Approximately 84 mL of blood will be collected during Cycle 2
- Approximately 56 mL of blood will be collected at Cycle 3
- Approximately 64 mL of blood will be collected at Cycle 4
- Approximately 56 mL of blood will be collected at Cycle 5
- Approximately 56 mL of blood will be collected at Cycle 6
- Approximately 38 mL of blood will be collected at EOT depending on the local lab.
- Approximately 38 mL of blood will be collected at the visit during the observation period.

In addition, approximately 20 mL of blood could be collected for an RCL sample during this study.

8 PARTICIPANT DISCONTINUATION

Refer to [Section 10.1.9 Study and Site Start and Closure] regarding discontinuation of study sites or of the study as a whole.

8.1 Discontinuation of Individual Participant(s) from Study Treatment

A discontinuation from treatment is defined as a participant who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The participant is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the participant from study treatment or to terminate a participant's involvement in the study at any time if the participant's clinical condition warrants it.

The reason for discontinuation from study treatment must be documented in the participant's medical records.

A participant must discontinue study treatment for any of the following reasons:

- Participant requests to stop treatment.
- Any clinical AE, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued treatment is not in the best interest of the participant.
- Participant is found to have significantly deviated from any one of the inclusion or exclusion criteria after enrollment (participants having clinical benefit and no DLT may be kept in the study after discussion with the medical monitor).
- Participant not achieving response (CR or PR) and the participant is no longer deriving clinical benefit, in the opinion of the investigator.

- Participant begins other anti-cancer therapies.
- Participant is in need of receiving prohibited concomitant treatment(s) based on Investigator's clinical opinion.
- Participant experiences disease relapse/progression.
- Investigator/subinvestigator determines that the continuation of the study treatment will be detrimental to the participant.
- Participant is lost to follow-up despite reasonable efforts by the investigator to locate the participant.
- Female participant becomes pregnant.
- Death.

8.2 Discontinuation of Individual Participant(s) from Study

All participants who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in the schedules of assessments [Table 3 to Table 6]. The only exception to this is when the participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

All participants who discontinue study treatment are to be followed for up to 12 months after their end of treatment, death or the final analysis, whichever occurs first per the schedules of assessments [Table 3 to Table 4].

8.3 Lost to Follow-up

Every reasonable effort is to be made to contact any participant lost to follow-up during the course of the study to complete study-related assessments, record outstanding data and retrieve IP. These contact attempts should be documented in the participant's medical record.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The hypotheses for the primary efficacy endpoint for each indication and dose level are given as follows:

Monotherapy Dose Expansion:

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

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

Combination Therapy Dose Expansion:

Metastatic Melanoma CPI Naïve

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

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

Metastatic Melanoma CPI Refractory

H0: iORR is 13%, at which the treatment is deemed as unacceptable.

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

Ovarian

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

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

Colorectal Cancer

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

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

9.2 Sample Size Determination

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.

Monotherapy

For each indication, with assumptions mentioned in the statistical hypotheses section, the statistical power would be approximately 0.80 while controlling the type I error rate at 0.05 (1-sided).

Combination Therapy

For each indication, with assumptions mentioned in the statistical hypotheses section, the statistical power would be approximately 0.80 while controlling the type I error rate at 0.05 (1-sided).

9.3 Populations for Analyses

The following populations are defined:

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 RAS 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 one 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 by 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.

DLT: dose limiting toxicity

9.4 Statistical Analyses

A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. Changes from the planned analyses in the final SAP that impact the statistical analyses will be justified in the clinical study report (CSR).

9.4.1 General Considerations

In general, data will be summarized with descriptive statistics for continuous endpoints, and frequency and percentage for categorical endpoints, unless otherwise specified. Percentages by categories will be based on the number of participants with no missing data (i.e., will add up to 100%).

Baseline will be defined as the last non-missing observation prior to first administration of IP, unless otherwise specified.

Demographics and baseline characteristics will be summarized by monotherapy and combination therapy arms, and dose level, and overall for all treated participants.

The number and percentage of participants who completed and discontinued treatment and reasons for treatment discontinuation will be presented for all enrolled participants and for participants in the safety analysis set (SAF) by monotherapy and combination therapy arms, and dose level, and overall. Similar tables for screening disposition, observation period disposition and follow-up disposition will also be presented for all treated participants by monotherapy and combination therapy arms, and dose level, and overall. All disposition details and dates of first and last evaluations for each participant will be listed.

Previous and concomitant treatment and medical history will be listed. Investigational product exposure will be summarized by descriptive statistics and will be listed.

9.4.2 Analysis of Efficacy

Binary efficacy endpoint analysis will be conducted on RAS while time to event endpoints will be conducted on FAS. The interpretation of results of the primary efficacy endpoint will be based on RAS. Efficacy analyses will be summarized by monotherapy and combination therapy and dose level. Tumor related analyses are summarized based on RECIST v1.1 and iRECIST.

9.4.2.1 Analysis of Primary Endpoint

9.4.2.1.1 Primary Analysis

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 by independent central review. iORR for each dose level will be calculated and its 95% confidence interval will be constructed by Clopper-Pearson method.

9.4.2.2 Sensitivity Analysis

The same analysis of the primary endpoint as described in [Section 9.4.2.1.1 Primary Analysis] will be conducted for the following:

- iORR with unconfirmed response by independent central review
- iORR with confirmed response by investigator assessment
- iORR with unconfirmed response by investigator assessment

9.4.2.3 Analysis of Secondary Endpoints

Objective Response Rate per RECIST v1.1 (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. The same analysis of the primary endpoint as described in [Section 9.4.2.1.1 Primary Analysis] will be conducted for the following:

- ORR with confirmed response by independent central review
- ORR with unconfirmed response by independent central review
- ORR with confirmed response by investigator assessment
- ORR with unconfirmed response by investigator assessment

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. iDCR for dose level will be calculated and its 95% confidence interval will be constructed by Clopper-Pearson method by independent central review and investigator assessment.

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. DCR for dose level will be calculated and its 95% confidence interval will be constructed by Clopper-Pearson method by independent central review and investigator assessment.

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). The distribution of OS will be estimated for each dose level using Kaplan-Meier methodology.

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 independent central review and investigator assessment, whichever occurs first. The distribution of iPFS will be estimated for each dose level using Kaplan-Meier methodology.

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 independent central review and investigator assessment, whichever occurs first. The distribution of PFS will be estimated for each dose level using Kaplan-Meier methodology.

Duration of Response per iRECIST (iDOR):

iDOR will be calculated only for the subgroup of participants with confirmed response iCR/iPR per iRECIST by independent central review and investigator assessment. The distribution of iDOR will be estimated for each dose level using Kaplan-Meier methodology.

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

DOR will be calculated only for the subgroup of participants with confirmed response CR/PR per RECIST v1.1 by independent central review and investigator assessment. The distribution of DOR will be estimated for each dose level using Kaplan-Meier methodology.

9.4.3 Analysis of Safety

Safety analyses will be conducted on the SAF. Safety analyses will be summarized by monotherapy and combination therapy arms, and dose level and overall.

9.4.3.1 Adverse Events

AEs will be coded using MedDRA and graded using NCI-CTCAE v5.0.

A TEAE is defined as an AE observed after starting administration of the IP until 30 days after the final administration of IP. An IP-related TEAE is defined as any TEAE with a causal relationship assessed as "yes" by the investigator.

The number and percentage of participants with TEAEs, drug-related TEAEs, serious TEAEs, drug-related serious TEASs, TEAEs leading to withdrawal of treatment and drug 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.

AE data will be listed.

9.4.3.2 Laboratory Assessments

For quantitative clinical laboratory measurements (hematology and biochemistry), descriptive statistics will be used to summarize results and change from baseline by monotherapy and combination therapy arms, and dose level, and overall and time point. Shifts from baseline to the worst grade based on NCI CTCAE 5.0 in laboratory tests will also be tabulated.

Laboratory data will be listed.

9.4.3.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline for participants in the SAF by dose level and time point.

Vital signs data will be listed.

9.4.3.4 Electrocardiogram

9.4.3.4.1 Routine 12-lead Electrocardiogram

The routine 12-lead ECG results will be summarized by monotherapy and combination therapy arms, dose level and time point.

Interpretations of routine 12-lead ECG results will be summarized by monotherapy and combination therapy arms, dose level and time point.

12-lead ECG data interpretations and quantitative values will be listed.

9.4.3.5 Eastern Cooperative Oncology Group Performance Status

Summary statistics (number and percent of participants) for each category of the ECOG performance status at each assessment will be provided. The change from baseline to final visit or early termination will also be summarized. Negative change scores indicate an improvement. Positive scores indicate a decline in performance.

9.4.3.6 Concentration-response Relationship Analysis

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

9.4.4 Analysis of Pharmacokinetics

Cellular DNA load and kinetic parameters for ASP7517 pharmacokinetics will be summarized by using descriptive statistics including n, mean, standard deviation, minimum, median, maximum, coefficient of variation (CV), geometric mean, and geometric CV. Time-course of cellular DNA load will be plotted as appropriate. Participants with sufficient cellular DNA samples will have kinetic parameter estimates for ASP7517 including calculation of AUC (including AUC_{last}, AUC_{28d}, AUC_{inf}), C_{max}, C_{trough} and t_{max} using standard noncompartmental analysis. For pharmacokinetic parameter, t_{max}, only n, median, minimum and maximum will be calculated.

Descriptive statistics of pembrolizumab pharmacokinetics may be tabulated.

9.4.5 Analysis of Pharmacodynamics Activities

Descriptive statistics will be provided for pharmacodynamics parameters whenever applicable. Exploratory analysis of the relationship between pharmacodynamic measurements and pharmacokinetics, efficacy and safety profile in participants may be performed.

9.4.5.1 Analysis of Exploratory Biomarker(s)

Associations between biomarkers and clinical results (efficacy, safety or pharmacodynamics) may be performed on participants who have the necessary baseline and on-study measurements to provide interpretable results for specific parameters of interest. Biomarkers may be summarized graphically or descriptively as they relate to clinical measures, as applicable. Summary statistics may be tabulated. Additional post-hoc analyses, such as alternative modeling approaches, may be conducted. All analyses described in this section are based on availability of the data.

9.5 Interim Analysis

Safety, pharmacokinetic and other clinical data will be reviewed on an ongoing basis to determine if the study will proceed on to the next dose level/phase.

For phase 2, according to the BOP2 design, the futility analysis for efficacy will be performed at the end of stage 1. If the response rate does not meet the optimal stopping boundaries, then stage 2 will be opened.

The safety in phase 2 will be monitored using Bayesian logistic model based on all DLT data obtained at the time of the analysis for both escalation and expansion cohorts and drug-related TEAEs leading to death. Safety monitoring with these models will start when phase 2 is opened. Enrollment in phase 2 may be held based on the following 2 criteria:

1. If the posterior mean of the safety event rate is higher than 30% as indicated by Bayesian logistic model across all tumor types at a given dose level for monotherapy or

combination therapy, then enrollment may be held in all expansion cohorts at that dose level and at higher dose levels for that therapy.

2. Additionally, if the posterior mean of the safety event rate is higher than 30% as indicated by Bayesian logistic model in a specific tumor type at a dose level for monotherapy or combination therapy, enrollment of that dose level and any higher dose-level may be held for that tumor type and that therapy.

9.6 Additional Conventions

If the start and stop dates of AEs and concomitant medications are incomplete, imputed dates will be used to determine whether an AE is/is not treatment emergent or to allocate a concomitant medication to the study period it was taken.

See the SAP for details of the definition for analysis windows to be used for analyses by visit/time point.

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medications if they are missing on day of first IP administration. The imputed dates will be used to assess if the AEs or concomitant medications are treatment emergent or concomitant, respectively. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Ethical, Regulatory and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent of Participants

10.1.3.1 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

10.1.3.2 Supply of New and Important Information Influencing the Participant's Consent and Revision of the Written Information

- The investigator or his/her representative will immediately inform the participant verbally whenever new information becomes available that may be relevant to the participant's consent or may influence the participant's willingness to continue participating in the study (e.g., report of serious adverse drug reaction). The communication must be documented in the participant's medical records and whether the participant is willing to remain in the study or not must be confirmed and documented.
- The investigator must update the participant's ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the participant on all updated ICFs throughout their participation in the study. The investigator or his/her designee must reconsent participants with the updated ICF even if relevant information was provided verbally. The investigator or his/her representative who obtained the written informed consent and the participant should sign and date the ICF (or for **Japan Region** place a personal seal). A copy of the signed (or for **Japan Region** sealed) ICF will be given to the participant and the original will be placed in the participant's medical record. An entry must be made in the participant's records documenting the reconsent process.

10.1.4 Data Protection

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless the participant provides written consent or approval. Additional medical information may be given only after approval of the participant to the investigator or to other appropriate medical personnel responsible for the participant's well-being.

The sponsor shall not disclose any confidential information on participants obtained during the performance of their duties in the study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to a participant's privacy due to direct access to source documents, or from other sources, they may not disclose the content to third parties.

The sponsor affirms the participant's right to protection against invasion of privacy. Only a participant identification number will identify participant data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then the sponsor shall serve as the controller of such data, as defined by the EU Data Protection Directive (DPD), and investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data. If the sponsor is not based in the EEA, the sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the DPD.

10.1.5 Committee(s) Structure

10.1.5.1 Dose Escalation and Safety Committee

A DESC consisting of sponsor representatives and investigators will convene once a dose level cohort completes the DLT observation period and data are available for review. Additional details regarding responsibilities, membership requirements and safety review time points are included in the DESC Charter. The DESC will also review the aggregate safety data from the phase 1 dose escalation and phase 2 expansion cohorts.

For full information regarding the membership, operations and logistics of the committee please refer to DESC Charter.

10.1.6 Dissemination of Clinical Study Data

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final CSR that forms part of a marketing authorization application, be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator(s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for the coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on the eCRF unless transmitted to the sponsor or designee electronically in an external data file (e.g., central laboratory data). The investigator is responsible for verifying that data entries on the eCRF are accurate and correct by physically or electronically signing the eCRF.
- Guidance on completion of eCRFs will be provided in a separate eCRF Completion Guideline.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of

noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator according to ICH or applicable local regulatory requirements, whichever is longer, after study completion. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source Documents

1. Source data must be available at the study site to document the existence of the participants and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.
2. The investigator must maintain accurate documentation (source data) that supports the information entered on the eCRF.
3. The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, electronic clinical outcome assessment and/or drug accountability.
4. Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information, if applicable). All printed records must be kept in the participant file and be available for archiving.
5. Study monitors will perform ongoing source data review and verification, as required by region, to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

UNIQUE to Japan Region:

The following are the major documents to be retained at the study site.

1. Source documents (clinical data, documents and records for preparing the eCRF) hospital records, medical records, test records, memoranda, checklists for evaluation, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, participant files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as participant registration forms, laboratory test slips including central measurement, worksheets specified by the sponsor, records of clinical coordinators, and records related to the study selected from those verified in other departments or hospitals.
2. Study contracts, written ICFs, written information and other documents or their copies prepared by the study personnel. A letter of request for study (including a request for continuation/amendment), letter of request for review, notice of study contract, study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), curriculum vitae of investigators, list of subinvestigators, list of signatures and print of seals (copy) and eCRF (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a study whose period exceeds one year or the adequacy of continuously conducting the study from which information on adverse drug reactions is obtained, and other documents obtained. A finalized protocol (including revisions), finalized Investigator's Brochure (including revisions), operational procedures for the investigator, materials and information supplied by the sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation) and the review result report of the IRB (including continuous deliberation), etc.
4. Records of control for IP and other duties related to the study. Procedure for controlling the IP, drug inventory and accountability record, vouchers for the receipt and return of the IP, and the prescriptions for concomitant medications

10.1.9 Study and Site Start and Closure

The study start date is the date the first participant signs the ICF for the study.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study test product development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor or designee shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Arrangement for Use of Information and Publication of the Study

Information concerning the test product, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the study in connection with the development of the product and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the study agreement.

10.1.11 Insurance of Participants and Others (*UNIQUE to Japan*)

If a participant suffers any study-related injury, the sponsor will compensate the participant appropriately according to the severity and duration of the damage. However, if the injury was caused intentionally or was due to gross negligence by the study site, the sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1. If a participant incurs an injury as a result of participation in the study, the study site should provide medical treatment and other necessary measures. The sponsor should be notified of the injury.

2. When the participant claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the sponsor. Both parties should work together towards a compensation settlement.
3. The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the study contract.
4. The sponsor shall make an arrangement for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

10.1.12 Quality Assurance

The sponsor is implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the study at any or all study sites and facilities. The audit may include on-site review of regulatory documents, eCRFs and source documents. Direct access to these documents will be required by the auditors.

To support quality around participant safety and reliability of study results, quality tolerance limits (QTLs) are defined and monitored. QTLs represent the acceptable variation of study data, taking into consideration the current state of medical and statistical knowledge about the variables to be analyzed, as well as the statistical design of the study. It is a level, point, or value associated with a parameter that should trigger an evaluation if a deviation is detected to determine if there is a possible systematic issue (i.e., a trend has occurred). The QTLs defined for this study are provided below.

Table 11 Quality Tolerance Limits

QTL #: Name and Parameter	Definition	Parameter Justification
QTL1: Eligibility: % or randomized participants not meeting key criteria	Proportion (%) of randomized participants with per-defined key inclusion/exclusion criteria deviation(s) that lead to exclusion from the per protocol population	A high number of participants not meeting the entrance criteria can have a negative impact on the interpretation of the primary analysis and overall validity of the trial results
QTL2: Late SAE reporting: % of SAEs reported > 1 days	Proportion (%) of SAEs reported more than one day after site awareness	Late SAE reporting may be an indicator of insufficient safety event reporting, missing safety events, and/or poor protocol compliance

QLT: quality tolerance limit; SAE: serious adverse event
Additional information regarding the QTL limit and limit justification, as well as associated activities can be found in STL-3458 QTL monitoring plan.

QTL Management Activities:

- For control of risks associated with "QTL1: Eligibility," refer to [Section 7.1 Efficacy Assessments]. For control of risks associated with "QTL2: Late SAE reporting," refer to [Section 7.3 Adverse Events and Other Safety Aspects] and [Section 10.3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting].

10.2 Appendix 2: Contraception Requirements

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the schedule of assessments. Pregnancy test results must confirm that the participant is not pregnant.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A female is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.

Females in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal with 1 of the following (i.e., permanently sterile):
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal

A postmenopausal state is defined as at least 12 months after last menstrual bleeding without an alternative medical cause.

In case the last menstrual bleeding cannot be clearly determined, confirmation with more than one follicle-stimulating hormone (FSH) measurement of at least > 40 IU/L (or higher per local institutional guidelines) is required.

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment.

Documentation of any of these categories can come from the study site personnel's review of the female participant's medical records, medical examination or medical history interview.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

Female participants of childbearing potential are eligible for participation in the study if they agree to use one of the highly effective methods of contraception listed below from the time of signing the ICF and until the end of relevant systemic exposure, defined as 6 after the final IP administration.[a]

Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly)[b]:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Other combined (estrogen- and progesterone-containing) methods
  - Vaginal ring
  - Injectable
  - Implantable
  - Intrauterine hormone-releasing system or intrauterine device
  - Bilateral tubal occlusion
- Vasectomized partner
  A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the test product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. It is not necessary to use any other method of contraception when complete abstinence is elected.

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male participants with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 6 months after final drug administration.[a]

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator
- Use a condom
- Female partners of male participants who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

10.3.1 Definition of Adverse Events

AE Definition:

An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study IP, whether or not considered related to the study IP.

"Adverse event" means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study IP. This includes events related to the comparator and events related to the (study) procedures.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study IP administration even though it may have been present before the start of the study.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, biochemistry or urinalysis) or other safety assessment (e.g., vital signs, physical examination, ECGs or radiographic scans), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease, does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the participant's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

10.3.1.2 Potential Cases of Drug-induced Liver Injury

Refer to [Section 10.4 Appendix 4: Liver Safety Monitoring and Assessment] for detailed instructions on drug induced liver injury. Abnormal values in AST and/or ALT concurrent or with abnormal elevations in TBL that meet the criteria outlined in [Section 10.4 Appendix 4: Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 10.3.6 Reporting Procedures for Serious Adverse Events].

10.3.2 Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If an event is not an AE per definition in [Section 10.3.1 Definition of Adverse Events], then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

10.3.3 Assessment of Causality

- The investigator is obligated to assess the relationship between study IP and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study IP administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Following a review of the relevant data, the causal relationship between the IP and each (S)AE will be assessed by answering "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the IP?"

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a "reasonable possibility" that an (S)AE may have been caused by the IP (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the participant been administered IP?
- Plausibility (i.e., could the event been caused by the suspect IP? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and study data, etc.)
- Dechallenge/dose reduction/rechallenge:
  - Dechallenge: Did the (S)AE resolve or improve after only stopping the dose of the suspect drug without any treatment?
  - Dose reduction: Did the (S)AE resolve or improve after reducing the dose of the suspect drug?
  - Rechallenge: Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results: a specific lab investigation supports the assessment of the relationship between the (S)AE and the IP (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of IP exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc., and strength of the alternative explanation
- Temporal relationship between exposure to the IP and (S)AE onset and/or resolution. Did the (S)AE occur in a reasonable temporal relationship to the administration of the IP?
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausible will be provided.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. While it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the sponsor, the initial report should be submitted without delay (i.e., within 24 hours of awareness). With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal

relationship, a causality assessment of "no" is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

10.3.4 Assessment of Severity

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute-common terminology criteria for adverse event (NCI-CTCAE) guidelines, version 5.0. The items that are not stipulated in the NCI-CTCAE, version 5.0 will be assessed according to the criteria below and entered into the eCRF:

Table 12 Grading Scale Defining the Severity of an Adverse Event

Grade	Assessment Standard
1 - Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2 - Moderate	Minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL†
3 - Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization indicated; disabling; limiting self-care ADL‡
4 - Life-threatening	Life-threatening consequences, urgent intervention indicated
5 - Death	Death related to AE

ADL: activities of daily living; AE: adverse event

†Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

‡Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

10.3.5 Recording and Follow-up of AEs and/or SAEs

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the sponsor in lieu of completion of the eCRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.6 Reporting Procedures for Serious Adverse Events

The investigator must complete and submit an SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor by fax or email immediately (within 24 hours of awareness).

The SAE worksheet must be signed by a medically qualified investigator (as identified on delegation of authority log). Signature confirms accuracy and completeness of the SAE data, as well as the investigator causality assessment including the explanation for the causality assessment.

For contact details, see [Contact Details of Sponsor's Key Personnel]. Fax or email the SAE/special situations/product defect worksheet to:

Astellas Pharma Global Development Inc.
Pharmacovigilance
North America fax number: +1-888-396-3750
North America alternate fax number: +1-847-317-1241
Email: safety-us@astellas.com

UNIQUE to Japan Sites:

In the case of a SAE, the investigator or subinvestigator must report to the head of the study site and must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU OYOBI FUGUAI HOUKOKUSHO or JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing

all information that is required by the appropriate regulatory authorities to the sponsor by fax or email immediately (within 24 hours of awareness) and to the head of the hospital.

For contact details, see [Contact Details of Sponsor's Key Personnel]. Fax or email the JUTOKUNA YUUGAIJISHOU OYOBI FUGUAI HOUKOKUSHO or JUTOKUNA YUUGAIJISHOU HOUKOKUSHO and special situations worksheet to:

Astellas Pharma Inc. – Japan
Pharmacovigilance
Fax number 03-3243-5747
Email: rk-safety-jp@jp.astellas.com

If there are any questions, or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or their designee [Contact Details of Sponsor's Key Personnel].

Follow-up information for the event should be sent promptly (as soon as available, but no longer than within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/special situation worksheet and on the eCRF.

The following minimum information is **required**:

- International study number/study number
- Participant number, sex and age
- Date of report
- Description of the SAE (event and seriousness criteria)
- Causal relationship to the IP (including reason)
- Drug provided (if any)

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g., SUSAR reporting) according to current local/regional regulatory requirements. The sponsor or sponsor's designee will submit expedited safety reports to competent authorities and concerned ethics committee per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (e.g., EMA, FDA) where required. Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the study site. In the US, FDA expedited IND reporting guidelines will be followed.

The sponsor will notify all investigators responsible for ongoing clinical studies with the test product of all SUSARs, which require submission per local requirements IRB/IEC/head of the study site.

The heads of the study sites/investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the rights, safety or well-being of the participant.

10.3.7 Reporting Procedures for Special Situations

10.3.7.1 Contraceptive Guidance and Collection of Pregnancy Information

If a female participant becomes pregnant during the study dosing period or within 180 days from the discontinuation of dosing, the investigator is to report the information to the sponsor according to the timelines in **[**Section 10.3.6 Reporting Procedures for Serious Adverse Events] using the SAE worksheet or pregnancy form as a special situation and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male participant who becomes pregnant during the study dosing period or within 180 days from the discontinuation of dosing and report the information to the sponsor according to the timelines in [Section 10.3.6 Reporting Procedures for Serious Adverse Event**s**] using the special situation worksheet or pregnancy form.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data, etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female participant as an AE in the eCRF or SAE per [Section 10.3.6 Reporting Procedures for Serious Adverse Events]. Participant pregnancy outcomes listed below are to be reported as SAEs:

- Spontaneous abortion/miscarriage, abortion and missed abortion
- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the IP.
- If an infant dies more than 1 month after the birth, it is to be reported if a relationship between the death and intrauterine exposure to the IP is judged as *"*possible*"* by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)
- Benign hydatidiform mole
- Blighted ovum

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination or other means as appropriate. (S)AEs experienced by the newborn/infant should be reported via the pregnancy reporting form. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date.

10.3.7.2 Medication Error, Overdose and "Off-label Use"

If a medication error (defined as an unintended failure in the treatment process that leads to, or has the potential to lead to, harm to the participant), overdose or "off-label use" (i.e., use outside of the target disease defined in the protocol) is suspected, refer to [Section 6.7

Treatment of Overdose]. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with the details of the medication error, overdose and/or "off-label use."

10.3.7.3 Misuse/Abuse

Definition of misuse: Situations where the IP is/are intentionally and inappropriately used not in accordance with the intended use as defined in the protocol.

Definition of abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

If misuse or abuse of the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with details of the misuse or abuse of the IP.

10.3.7.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the IP of study site personnel while preparing it for administration to the participant) to the IP occurs, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the special situation are to be reported on the special situations worksheet.

10.3.7.5 (Suspicion of) Transmission of Infectious Agent

If transmission of an infectious agent associated with the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness) and any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with the details of the suspected transmission of infectious agent.

10.3.7.6 Suspected Drug-drug Interaction

If a drug-drug interaction associated with the IP is suspected, the investigator must forward the special situation worksheet to the sponsor by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of an SAE, the SAE is also to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events] together with details of the suspected drug-drug interaction.

10.3.7.7 Reporting Procedures for Product Defect

When investigator-confirmed death or SAE caused by a defect of a regenerative medicine product occurs, or when the investigator judges there is a risk that the product defect caused a SAE, the (suspected) product defect is to be reported to sponsor.

The investigator must complete and submit a product defect worksheet containing all information that is required by local and/or regional regulations to the sponsor by fax or email immediately (within 24 hours of awareness). The product defect worksheet is to be reported as described in [Section 10.3.6 Reporting Procedures for Serious Adverse Events].

10.3.8 Supply of New Information Affecting the Conduct of the Study

When new information becomes available that is necessary for conducting the study properly, the sponsor will inform all investigators involved in the study as well as the appropriate regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the participants, who will be required to sign an updated ICF in order to continue in the study.

UNIQUE to Japan Region:

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 80-2 Paragraph 6 of the Pharmaceutical Affairs Law, the sponsor should inform all investigators involved in the study, head of the study site and appropriate regulatory authorities of such information. The head of the study site who receives such information will decide whether the study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the participants, in compliance with [Section 10.1.3.2 Supply of New and Important Information Influencing the Participant's Consent and Revision of the Written Information].
2. In addition, when the head of the study site receives the revisions of the Investigator's Brochure, protocol, written information, information on the matters covering the quality of the test product, efficacy and safety, information necessary for conducting the study properly or documents to be examined by the IRB, these documents should be sent to the IRB.
3. When the sponsor receives a safety issue from any source either Japan or worldwide that requires an urgent safety measure (USM) to be implemented, then the sponsor will report that safety information to all study sites in Japan and the rest of the world (within 24 hours of awareness).

10.3.8.1 Collection of Defect Information in Stage of Manufacture, Delivery and Storage

Provision of information from QA to Pharmacovigilance (PV):

- If QA determines that there is a significant quality issue in the defect information collected after shipment of the investigational products, QA will send it to PV. When it is judged as a significant quality issue, the impact on the participant is also evaluated by QA, therefore PV evaluates the provided information and reports it to the Pharmaceutical and Medical Devices Agency (PMDA).

Provision of information from the PV department to the QA department:

- When the defect information is reported to PV from the investigational sites, PV will send it to QA. If QA obtains the follow-up information, QA will send it to PV and PV will submit the additional report to PMDA.

10.3.9 Urgent Safety Measures

A USM is an intervention that is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant competent authorities, IRB/IEC, where applicable, in order to protect participants from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate a USM. The cause of a USM can be safety-, product- or procedure-related.

When the sponsor receives a safety issue from any source (either Japan or worldwide) that requires a USM to be implemented, then the sponsor will report that safety information to all study sites in Japan and the rest of world (within 24 hours of awareness).

10.3.10 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the study physician and/or (for **Japan region)** an Astellas team member (within 24 hours of awareness). Full details of the potential USM are to be recorded in the participant's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be a USM, the sponsor will take appropriate action to ensure the safety and welfare of the participants. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

10.4 Appendix 4: Liver Safety Monitoring and Assessment

The purpose of this appendix is to provide guidance for the monitoring of drug-induced liver injury during the course of the study. It should be noted that this section does not specify the end-of-study analyses of liver enzymes. The end-of-study liver enzymes analyses will be described in the SAP. Any participant enrolled in a study with active drug therapy and reveals an increase of serum aminotransferases (AT) to > 3 × ULN or bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least alkaline phosphatase [ALP], ALT, AST and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator and study team. Participants should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN is as shown below.

Table 13 Moderate and Severe Liver Abnormalities

	ALT or AST		TBL
Moderate	> 3 × ULN	or	> 2 × ULN
Severe	> 3 × ULN	and†	> 2 × ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal

†Samples taken simultaneously or within maximum 24 hours.

In addition, the participant should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks.
- ALT or AST > 3 × ULN and† TBL > 2 × ULN or international normalized ratio (INR) > 1.5 (if INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and† (TBL > 2 × ULN in participants with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

† Samples taken simultaneously or within a maximum of 24 hours.

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and clinical laboratory tests. The study site personnel are to complete

the liver abnormality case report form (LA-CRF). Participants with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal liver function tests should be repeated 2 to 3 times weekly, and then weekly or less if abnormalities stabilize or the IP has been discontinued and the participant is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all participants for whom severe hepatic liver function abnormalities possibly attributable to IP are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases are to be recorded as "AEs" within the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic participants, and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications are to be entered in the eCRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the participant's history, other testing may be appropriate including:
  - Acute viral hepatitis (A, B, C, D, E or other infectious agents)
  - Ultrasound or other imaging to assess biliary tract disease
  - Other clinical laboratory tests, including INR and direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased liver function tests, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the participant may be discontinued from study treatment. The investigator may determine that it is not in the participant's best interest to continue study treatment. Discontinuation of study treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and† TBL > 2 × ULN or INR > 1.5) (if INR testing is applicable/evaluated)

- ALT or AST > 5 × ULN and† (TBL > 2 × ULN in participants with liver metastases)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

† Samples taken simultaneously or within a maximum of 24 hours.

In addition, if close monitoring for a participant with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

Hy's Law definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% to 50% mortality (or transplant).

The 2 "requirements" for Hy's Law are:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in AT elevations > 3 × ULN ("2 × ULN elevations are too common in treated and untreated participants to be discriminating").
2. Cases of increased TBL (at least 2 × ULN) with concurrent AT elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

FDA Guidance for Industry titled, "Drug-induced Liver Injury: Premarketing Clinical Evaluation" issued by the FDA on July 2009:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among participants showing such AT elevations, often with ATs much greater than 3 × ULN, one or more also show elevation of serum TBL to > 2 × ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

10.5 Appendix 5: List of Excluded Concomitant Medications

10.5.1 Concomitant Medications

The following list describes concomitant medications that are prohibited. This list should not be considered all inclusive. If there are concerns or questions about concomitant use of any drugs listed below, discussion with the medical monitor is strongly encouraged.

Drug Type	Generic Drug Name
Corticosteroids*	Dexamethasone Prednisone (Deltasone, Orasone, Predone, RAYOS, Sterapred, etc.)
Interferon/polyethylene-interferon	
Immunosuppressive Agents	Abatacept (Orencia, etc.) Adalimumab (Humira, etc.) Anajunra (Kineret, etc.) Azathioprine (Azasan, Imuran, etc.) Budesonide (Entocort EC, etc.) Certolizumab (Cimzia, etc.) Cyclosporine (Neoral, Sandimmune, SangCya, etc.) Etanercept (Enbrel, etc) Everolimus (Afinitor, Zortress, etc.) Golimumab (Simponi, etc.) Infliximab (Remicade, etc.) Ixekizumab (Taltz, etc.) Leflunomide (Arava, etc.) Mycophenolate (CellCept, Myfortic, etc.) Natalizumab (Tysabri, etc.) Prednisolone (Millipred, etc.) Rituximab (Rituxan, etc.) Secukinumab (Cosentyx, etc.) Sirolimus (Rapamune, etc.) Tocilizumab (Actemra, etc.) Tofacitinib (Xeljanz, etc.) Ustekinumab (Stelara, etc.) Vedolizumab (Entyvio, etc.)

*The use of high dose system corticosteroids is prohibited, with the exception of immune-related AEs.

10.5.2 Other Investigational Agents

Treatment with investigational agents other than ASP7517 is prohibited. If there are concerns or questions about concomitant use of these drugs, discussion with the co-chairs and protocol officer is strongly encouraged.

10.6 Appendix 6: Clinical Laboratory Assessments

Laboratory tests will be performed according to the schedule of assessments.

Table 14 Clinical Laboratory Tests

Panel/Assessments	Parameters to be Analyzed
Hematology	Hematocrit (Hct) Hemoglobin (Hgb) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Platelet count Red blood cell count (RBC) White blood cell count (WBC) White blood cell count differential
Chemistry	Sodium (Na) Potassium (K) Chloride (Cl) Bicarbonate (HCO3) or CO2† Blood urea nitrogen (BUN) Creatinine (Cr) Glucose (Gl) Calcium (Ca) Phosphate (Pi) Magnesium (Mg) Albumin (Alb) Total protein (T Prot) Alkaline phosphatase (ALP) Lactate dehydrogenase (LDH) Creatine phosphokinase (CK) Liver function tests including: Bilirubin total (TBL) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST)
Table continued on next page	

Panel/Assessments	Parameters to be Analyzed
Urinalysis	Color Appearance Specific gravity pH Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite Protein Urobilinogen
Urine/Serum Pregnancy Test *	hCG
Coagulation Profile (PT/INR, D-Dimer, Fibrinogen)	Activated partial thromboplastin time (aPTT) International normalized ratio (INR) Prothrombin time (sec) (PT) Fibrinogen D-Dimer
Thyroid Panel	Triiodothyronine or free triiodothyronine Free thyroxine Thyroid stimulating hormone

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

† If testing is not available, this test is not mandatory.

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

10.7 Appendix 7: Pharmacogenomic Analysis With Banked Sample

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring differences in a participant's gene and/or expression of genes based on genetic variation may impact what treatment options are best suited for the participant. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association studies, the relationship between gene profiles and a drug's kinetics, efficacy, toxicity or disease may be better understood. As many diseases may be influenced by one or more genetic variations, PGx research may identify which genes are involved in determining the way a participant may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and/or toxicity/safety and/or disease.

By analyzing genetic variations, it may be possible to predict an individual participant's response to treatment in terms of efficacy and/or toxicity and/or disease.

PARTICIPANT PARTICIPATION

Participants who have consented to participate in this study will participate in the PGx substudy. Participants must provide written consent prior to providing any blood samples that may be used at a later time for PGx analysis.

SAMPLE COLLECTION AND STORAGE

Participants who consent to participate in this substudy will provide approximately 4 mL sample of whole blood/buccal swab per Astellas' instructions. Each sample will be identified by the unique participant number. Samples will be shipped to a designated banking CRO as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis if evidence suggests that genetic variants may be influencing the drug's pharmacokinetics, efficacy and/or safety and/or disease.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database lock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The participant has the right to withdraw consent at any time. When a participant's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely unless otherwise specified by local regulation.

INFORMATION DISCLOSURE TO THE PARTICIPANTS

Exploratory PGx analysis may be conducted following the conclusion of the study, if applicable. The results of the PGx analysis will not be provided to any investigators or participants, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

10.8 Appendix 8: Infusion Reaction Dose Modification and Treatment (Guidelines for ASP7517 and Pembrolizumab)

Table 15 Infusion Reaction Dose Modification and Treatment (Guidelines for ASP7517 and Pembrolizumab)

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 h.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Intravenous fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 h of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/h. to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment (pembrolizumab only)**	**Pembrolizumab only:** Participant may be premedicated 1.5 h (± 30 min) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic). Contact the study medical monitor regarding ASP7517 dose management
Table continued on next page		

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include, but is not limited to: o Epinephrine* o Intravenous fluids o Antihistamines o NSAIDs o Acetaminophen o Narcotics o Oxygen o Pressors o Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Once the participant has been stabilized, collect blood for cytokine/ chemokine panel (ad hoc collection for shipment to central lab). • **If the reaction is suggestive of anaphylaxis, collect blood (standard red top tube) for serum total tryptase level (levels typically peak within 3 h after the onset of symptoms). Serum should be frozen if the assay cannot be performed promptly at the local laboratory.** • **Hospitalization may be indicated.** *** In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.**	Any grade 4 hypersensitivity reaction/anaphylaxis, study treatment should be discontinued
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.		

NCI: National Cancer Institute; NSAID: non-steroidal anti-inflammatory drug

10.9 Appendix 9: Monitoring of Pembrolizumab Potential Immune-related Adverse Events

Table 16 Monitoring of Pembrolizumab Potential Immune-related Adverse Events

Potential irAE	Closely monitor participants' symptoms for prompt diagnosis and management.
Pneumonitis	New cough, worsening cough, shortness of breath, or chest pain
Colitis	Changes in bowel habits; abdominal pain; blood or mucus in stool; nausea
Hepatitis	Yellowing of skin or whites of eyes; pain on right side of abdomen; dark urine (color of tea); nausea or vomiting; bleeding or bruising more easily than usual; loss of appetite; drowsiness
Endocrinopathies	Persistent or unusual headaches, changes in vision, rapid heartbeat, increased sweating, feeling very tired or weak, achy muscles, change in weight (gain or loss), feeling lightheaded or feeling faint, feeling more hungry or thirsty than usual, loss of hair, mood changes such as reduced sex drive or increased irritability, forgetfulness, feeling cold, constipation, deeper voice, urinating more frequently than usual, nausea or vomiting, abdominal pain
Motor/sensory neuropathy; Encephalitis; Myasthenic syndrome/myasthenic gravis or Guillain-Barre syndrome	Numbness or tingling, weakness, confusion, headache, forgetfulness, changes in mood or behavior, fever, increased sensitivity to light, neck stiffness
Ocular Inflammation	Changes in vision (blurry vision; double vision; other vision changes), eye pain, eye redness, eyelid swelling
Pancreatitis	Nausea or vomiting, abdominal pain
Infection	Fever, other signs of infection
Musculoskeletal inflammation	New or worsening joint symptoms, muscle weakness or pain

irAE: immune-related adverse event

10.10 Appendix 10: Dose Modification and Toxicity Management for Immune-related AEs

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 17.

Based on the mechanism of action of ASP7517, immune-related adverse reactions (e.g., fever, headache, fatigue, hot flashes, diarrhea and muscular and joint pain) should be considered (see [Section 2.3.1.8 Other]) and managed as required per standard of care. In case of such events, ensure adequate evaluation to confirm etiology or exclude other causes. In addition, the study medical monitor should be contacted to discuss event monitoring, follow up and study treatment management.

Table 17 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

General instructions: 1. Severe and life-threatening immune-related adverse events (irAEs) should be treated with intravenous corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment. 3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.
Table continued on next page

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus) • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Table continued on next page

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides, as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders

Table continued on next page

Footnotes

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: > 3.0 - 5.0 × ULN if baseline normal; > 3.0 - 5.0 × baseline, if baseline abnormal; bilirubin: > 1.5 - 3.0 × ULN if baseline normal; > 1.5 - 3.0 × baseline if baseline abnormal

[b] AST/ALT: > 5.0 to 20.0 × ULN, if baseline normal; > 5.0 - 20.0 × baseline, if baseline abnormal; bilirubin: > 3.0 - 10.0 × ULN if baseline normal; > 3.0 - 10.0 × baseline if baseline abnormal

[c] AST/ALT: > 20.0 × ULN, if baseline normal; > 20.0 × baseline, if baseline abnormal; bilirubin: > 10.0 × ULN if baseline normal; > 10.0 × baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: common terminology criteria for adverse events; GI: gastrointestinal; irAE: immune-related adverse event; ULN: upper limit of normal

10.11 Appendix 11: Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 18.

Table 18 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 h of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/h. to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (± 30 min) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic).
Table continued on next page		

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine† • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. †In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

NCI: National Cancer Institute; NSAID: nonsteroidal anti-inflammatory drug

10.12 Appendix 12: Clinical Study Continuity

INTRODUCTION

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments (Table 1 to Table 5) unless the site principal investigator (PI) discusses the need with the Astellas medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in Section 4 due to a crisis.

INFORMED CONSENT

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent, which explicitly informs them of the nature of and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the PI or designee will obtain oral agreement from the participant followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.

PARTICIPANT PROCEDURES ASSESSMENT

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:

- Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible
- Site facilities have been closed for clinical study conduct.
- Site has been restricted to treating participants with conditions outside of the scope of the study.
- Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel.
- Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel.

- Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel.
- Participant has risk factors for which traveling to the site pose an additional risk to the participant's health and safety.

Adherence to the original protocol as reflected in the Schedule of Assessments (Section 1.3) is expected, where plausible, in the case of a crisis. The alternate measures as noted in Table 19 to Table 23 below are only permissible in the event of a crisis, and after discussing the need with the Astellas Medical Monitor to implement the alternate measures. This is to allow for continuity of receiving Investigational Medicinal Product (IMP) and maintaining critical safety and efficacy assessments for participants participating in the study at a time of crisis.

If one or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

ALTERNATIVE SCHEDULES OF ASSESSMENTS IN RESPONSE TO A CRISIS

Table 19 Study Interruption: Schedule of Assessments – Dose Escalation Cohort

	Alternate Approach(es)	Treatment[a]																EOT[t]
		Cycle 1					Cycle 2					Cycles 3–4[b]			Cycles 5–6[c]			
Visit Days		**1**	**2**	**4**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Window(days)		0	0	0	±1	±1	±1	0	±1	±1	±1	±3	±1	±1	±3	±1	±1	+7
Physical Examination[d]																		
Vital Signs	Except for IP administration days, exams can be performed at a local facility and results submitted to PI	X[e]	X	X	X	X	X[e]	X	X	X	X	X[e]	X	X	X[e]	X	X	X
ECOG Performance	Except for IP administration days, can be completed by remote/telemedicine visit	X[f]	X	X	X	X	X[f]		X	X	X	X[f]	X	X	X[f]	X	X	X
12-Lead ECG[h]	Except for IP administration days triplicate may be performed as possible at a local clinic and results submitted to PI. If cannot be performed, Astellas Medical Monitor to assess for study continuation.	X[h]				X	X[h]			X	X[h]	X[h]			X[h]			X
Prior and Concomitant Medications	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments Every Visit																	

Table continued on next page

Footnotes

	Alternate Approach(es)	Treatment[a]																EOT[t]
		Cycle 1					Cycle 2					Cycles 3–4[b]			Cycles 5–6[c]			
Visit Days		**1**	**2**	**4**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Window(days)		0	0	0	±1	±1	±1	0	±1	±1	±1	±3	±1	±1	±3	±1	±1	+7
Pregnancy Test for WOCBP	Test must be completed prior to dosing, however EOT test may be performed at local clinic and result submitted to PI	X[j]					X[j]					X[j]			X[j]			X[j]
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[k,f]	Except for IP administration days, collection of samples at local facility acceptable if results can be made available to investigative site																	
Coagulation Profile (PT/INR, D-dimer, fibrinogen)[k]	Except for IP administration days, collection of samples at local facility acceptable if results can be made available to investigative site	X[f]	X	X	X	X	X[f]	X	X	X	X	X[f]			X[f]			X
Thyroid Profile Panel[l]	Test to be completed for IP administration days in the clinic. EOT lab testing can be performed at a local clinic per protocol requirement, and results submitted to PI for evaluation	X									X	Every 6 weeks						X
IRT Transaction Required	None	X[m]					X					X			X			
AE/SAE Assessment	Completion by phone contact allowed for non-dosing visits with further assessment at local clinic if needed. ***Every Visit***																	
PGx[n]	None	X[n]																

Table continued on next page

Footnotes

	Alternate Approach(es)	Treatment[a]																EOT[t]
		Cycle 1					Cycle 2					Cycles 3–4[b]			Cycles 5–6[c]			
Visit Days		**1**	**2**	**4**	**8**	**15**	**1**	**2**	**4**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	
Window(days)		0	0	0	±1	±1	±1	0	±1	±1	±1	±3	±1	±1	±3	±1	±1	+7
Buccal Swab for HLA Typing	None	X[f]																
Pharmacokinetic: A7517[o]	None	X	See Table 6 in the Protocol for detailed sample time points															X
Pharmacokinetic: Pembrolizumab[o]	None:	X	See Table 6 for detailed sample time points															X
Anti-WT1 antibody	None	X[f]					X[f]					X[f]			X[f]			X
Immune Response Biomarker (ELISpot)	None	X[f]			X	X	X[f]			X	X	X[f]	X	X	X[f]	X	X	X
Immune Response Biomarker (Tetramer)	None:	X[f]				X	X[f]				X	X[f]		X	X[f]		X	X
Immune Cell Phenotyping	None:	X[f]			X	X	X[f]			X	X	X[f]	X	X	X[f]	X	X	X
Cytokines	None:	X[f]	X	X	X	X	X[f]	X	X	X	X	X[f]	X	X	X[f]	X	X	X
Circulating Tumor DNA	None:	X[f]					X[f]					X[f]			X[f]			X
Archival Tumor Tissue[p]	To be provided from archival tumor sample available	X																
Radiographic Disease Assessment[q]	Assessment to be done per protocol requirements. Outside of the window assessments need to be escalated to Astellas Medical Monitor	Every 56 ±7 days																
ASP7517 Dosing[r]	None.	X					X					X			X			
Pembrolizumab Dosing[s]	None	X									X[s]	Every 6 weeks[s]						

Footnotes appear on next page

AE: adverse event; C: Cycle; CR: complete response; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EOT: end of treatment; FFPE: formalin-fixed, paraffin-embedded; HLA: human leukocyte antigen; ICF: informed consent form; IP: investigational product; IRT: interactive response technology; MRI: magnetic resonance imaging; PGx: pharmacogenomic; PI: principal investigator; PR: partial response; PT/INR: prothrombin time/international normalized ratio; SAE: serious adverse event; Scr: screening; SD: stable disease; WOCBP: woman of childbearing potential; WT1: Wilms' tumor 1 protein.

a. Cycles 1 through 6 represent ASP7517 monotherapy or combination of ASP7517 and pembrolizumab therapy; each cycle is 28 days.
b. After the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as radiological response or SD, or reduction of disease-related symptoms) will continue further treatment of ASP7517 in cycles 3 and 4, as decided by the investigator.
c. After the first 4 cycles, participants who achieve PR or SD may receive 2 doses of ASP7517 in Cycles 5 and 6.
d. Height measurement performed at screening only. Height measurement may be performed at a subsequent visit if it was not done at screening. Weight measurement performed at screening and Day 1 of each cycle.
e. The following vital sign assessment schedules apply:
   - At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, vital signs are obtained predose (-1 h from start of pembrolizumab infusion), within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion, at the end of the pembrolizumab infusion (-5 to +10 min window), 30 min (± 10 min) after completion of the pembrolizumab infusion, within 15 min prior to the start of the ASP7517 infusion, every 15 min (5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to +10 min window), and postdose (+30 min, +1, +2, +3 and +4 h [± 10 min window each] from end of the ASP7517 infusion).
   - ASP7517 dosing only: Vital signs are obtained within 15 min prior to start of the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to +10 min window), as well as 30 min (± 5 min), 1 h (±10 min) and 2 h (± 10 min) after completion of the ASP7517 infusion. If participants are still available, additional optional vital sign assessments 3 h (± 10 min) and 4 h (± 10 min) after completion of the ASP7517 infusion will be obtained.
   - Pembrolizumab dosing only: Vital signs will be obtained 15 min prior to the start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion (-5 to +10 min window), at the end of the pembrolizumab infusion (-5 to + 10 min window) and at 30 min (±10 min) after completion of the pembrolizumab infusion for participants in the combination therapy.
f. Obtain predose.
g. If chest X-ray is performed within to 2 weeks of screening (prior to ICF and performed as part of standard of care), then it does not need to be repeated.
h. 12-lead ECGs will be recorded in triplicate (at least 2 min apart per time point) and transmitted electronically for central reading. ECGs may be repeated once during screening. On IP administration days, ECGs will be obtained:
   - At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of ASP7517.
   - ASP7517 dosing only: ECGs are obtained predose (-1 h from start of ASP7517 infusion) and 1 to 2 h post dose of ASP7517.
   - Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.
i. Includes medications taken within 28 days prior to C1D1. Include all anticancer treatment received 28 days prior to IP administration.
j. Urine or serum pregnancy test will be performed in WOCBP. On treatment visit days, test must occur prior to IP administration.
k. Laboratory tests will be analyzed by the institution's local laboratory. However, sample results must also be submitted for centralized data entry. Laboratory test may be repeated during the screening period.

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l. Thyroid panel including triiodothyronine or free triiodothyronine, free thyroxine and thyroid stimulating hormone will be measured prior to receiving pembrolizumab only for participants in the combination cohort (C1D1, C2D15, C4D1 and C5D15). If the thyroid panel is to be measured on same day of pembrolizumab dosing (ex. C4D1, pembrolizumab monotherapy dosing visit), the thyroid panel must be measured prior to receiving pembrolizumab. Thyroid panels assessed on C1D1 and C2D15 only apply for the combination therapy cohort.
m. Enrollment or randomization will be done via IRT system after confirmation of eligibility and prior to dosing.
n. Whole blood for optional PGx study may be collected at C1D1 prior to IP administration.
o. See Table 6 for collection schedule for ASP7517 monotherapy and ASP7517 and pembrolizumab combination therapy.
p. Archival tumor specimen at a minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 20 FFPE unstained serial slides are required.
q. Same technique (CT/MRI) used at screening should be utilized throughout the study. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the participant's disease. Scans performed prior to informed consent as standard of care are acceptable as screening scans, if done within 28 days prior to C1D1.
r. In both the monotherapy and combination cohorts, each participant must remain at the site facility for 4 h following the participant's first dose of ASP7517. For the next dose (2nd dose) or additional subsequent monotherapy with ASP7517, participants must remain at the site facility for at least 2 h after ASP7517 dosing.
s. In the combination therapy arm, pembrolizumab will be administered as an intravenous infusion over 30 min followed by ASP7517 administration at least 1 h after pembrolizumab administration.
t. If the participant will discontinue treatment due to meeting protocol criteria of CR after completion of Cycle 4 or a participant completes all 6 cycles of ASP7517, then all visits in the treatment cycle should be completed and the EOT visit will be performed 7 days (+ up to a 7-day window) after the last planned visit.
    - If participant has CR after completing Cycle 4, the EOT visit would be performed between C4D22 and C4D29.
    - If participant has SD or PR after completing Cycle 4, they are expected to complete all visits through C6D15 and the EOT visit would be performed between C6D22 and C6D29.
    - If the investigator decides to discontinue treatment prior to the completion of any cycle, the EOT visit will occur 7 days after the decision to discontinue treatment.
    - If new anticancer therapy is to be initiated, the EOT visit must occur prior to start of the new therapy, even if < 7 days from the decision to discontinue treatment.
    - For combination therapy participants that continue with pembrolizumab monotherapy, EOT visit will be performed 7 days after 17th dose of pembrolizumab or 7 days after decision to discontinue treatment, or prior to start of new anticancer therapy, whichever is earliest.

Table 20 Study Interruption: Schedule of Assessments for Dose Expansion Cohort

	Alternate Approach(es)	Treatment[a]												EOT[s]
		Cycle 1				Cycle 2				Cycles 3–4[b]		Cycles 5-6[c]		
		1	4	8	15	1	4	8	15	1	15	1	15	+7
Window(days)		0	±1	±1	±1	±1	±1	±1	±1	±3	±1	±3	±1	
Physical Examination[d]	For Cycle 1, each Cycle D1 are IP administration days. Other visits can be obtained at local facility and results submitted to PI													
Vital Signs[e]	Except for IP administration days, other exams can be performed at a local facility and results submitted to PI													
ECOG Performance[f]	Except for IP administration days, can be completed by remote/telemedicine visit													
12-Lead ECG[h]	Except for IP administration days triplicate may be performed as possible at a local clinic and results submitted to PI. If cannot be performed, Astellas Medical Monitor to assess for study continuation.	X[h]				X[h]				X[h]		X[h]		X
Prior and Concomitant Medications	Remote/Virtual/Telemedicine Visits allowed for non-dosing visits. Please refer to protocol schedule of assessments Every Visit	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test for WOCBP	Test must be completed prior to dosing, however EoT test may be performed at local clinical and result submitted to PI	X[j]				X[j]				X[j]		X[j]		X[j]
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[k]	Except for IP administration days, collection of samples at local facility acceptable if results can be made available to investigative site	X[f]		X	X	X[f]	X	X	X	X[f]	X	X[f]	X	X

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Footnotes

	Alternate Approach(es)	Treatment[a]												EOT[s]
		Cycle 1				Cycle 2				Cycles 3–4[b]		Cycles 5-6[c]		
		1	4	8	15	1	4	8	15	1	15	1	15	+7
Window(days)		0	±1	±1	±1	±1	±1	±1	±1	±3	±1	±3	±1	
Coagulation Profile (PT/INR, D-dimer, fibrinogen)[k]	Except for IP administration days, collection of samples at local facility acceptable if results can be made available to investigative site	X[f]		X	X	X[f]		X	X	X[f]	X	X[f]	X	X
Thyroid Profile Panel[l]	Except for IP administration days, the lab testing can be performed at a local clinic per protocol requirement communicated by the PI and results submitted to PI for evaluation	X							X	Every 6 weeks after C2D15 dose				X
PGx[m]	None	X[m]												
Buccal Swab for HLA Typing	None	X[f]												
AE/SAE Assessment	Completed by phone contact allowed for non-dosing visits with further assessment at local clinic if needed. ***Every visit***													
Pharmacokinetic: A7517[n]	None	X	See Table 6 for sample time points											X
Pharmacokinetic: Pembrolizumab[n]	None	X	See Table 6 for sample time points											X
Anti-WT1 antibody	None	X[f]				X[f]				X[f]		X[f]		X
Immune Response Biomarker (ELISpot)	None	X[f]		X	X	X[f]		X	X	X[f]	X	X[f]	X	X
Immune Response Biomarker (Tetramer)	None	X[f]			X	X[f]			X	X[f]	X	X[f]	X	X
Immune Cell Phenotyping	None	X[f]		X	X	X[f]		X	X	X[f]	X	X[f]	X	X
Cytokines	None	X[f]	X	X	X	X[f]	X	X	X	X[f]	X	X[f]	X	X

Table continued on next page

Footnotes

	Alternate Approach(es)	Treatment[a]												EOT[s]
		Cycle 1				Cycle 2				Cycles 3–4[b]		Cycles 5-6[c]		
		1	4	8	15	1	4	8	15	1	15	1	15	+7
Window(days)		0	±1	±1	±1	±1	±1	±1	±1	±3	±1	±3	±1	
Circulating tumor DNA	None	X[f]				X[f]				X[f]		X[f]		X
Archival Tumor Tissue[o]	To be provided from archival tumor sample available	X												
Tumor Tissue, Fresh Biopsy	None	X[q]							X[r]					
Radiographic Disease Assessment[p]	Assessment to be done per protocol requirements. Outside of the window assessments need to be escalated to Astellas Medical Monitor	Every 56 ±7 days												
ASP7517 Dosing	None	X				X				X		X		
Pembrolizumab Dosing	None	X							X	Every 6 weeks after C2D15 dose				

AE: adverse event; C: Cycle; CR: complete response; CT: computed tomography; D: Day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EOT: end of treatment; FFPE: formalin-fixed, paraffin-embedded; HLA: human leukocyte antigen; ICF: informed consent form; IP: investigational product; IRT: interactive response technology; MRI: magnetic resonance imaging; PGx: pharmacogenomic; PI: principal investigator; PR: partial response; PT/INR: prothrombin time/international normalized ratio; SAE: serious adverse event; Scr: screening; SD: stable disease; WOCBP: woman of childbearing potential; WT1: Wilms' tumor 1 protein.

a. Cycles 1 through 6 represent ASP7517 monotherapy or combination of ASP7517 and pembrolizumab therapy; each cycle is 28 days.

b. After the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit (defined as radiological response or SD, or reduction of disease-related symptoms) will continue further treatment of ASP7517 as decided by the investigator.

c. After the first 4 cycles, participants who achieve PR or SD may receive 2 doses of ASP7517 in Cycles 5 and 6.

d. Height measurement performed at screening only. Height measurement may be performed at a subsequent visit if it was not done at screening. Weight measurement performed at screening and Day 1 of each cycle.

e. The following vital sign assessment schedules apply:

- At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, vital signs are obtained predose (-1 h from start of pembrolizumab infusion), within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion, at the end of the pembrolizumab infusion (-5 to +10 min window), 30 min (± 10 min) after completion of the pembrolizumab infusion, within 15 min prior to the start of the ASP7517 infusion, every 15 min (5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to +10 min window), and post-dose (+30 min, +1, +2, +3 and +4 h [± 10 min window each] from end of the ASP7517 infusion).

Footnotes continued on next page

- ASP7517 dosing only: Vital signs are obtained within 15 min prior to start of the pembrolizumab infusion, every 15 min (-5 to +10 min window) during the ASP7517 infusion, , every 15 min (-5 to +10 min window) during the ASP7517 infusion, at the end of the ASP7517 infusion (-5 to + 10 min window), as well as 30 min (± 5 min), 1 h (± 10 min) and 2 h (± 10 min) after completion of the ASP7517 infusion. If participants are still available, additional optional vital sign assessments 3 h (± 10 min) and 4 h (± 10 min) after completion of the ASP7517 infusion will be obtained.
- Pembrolizumab dosing only: Vital signs will be obtained within 15 min prior to start of the pembrolizumab infusion, 15 min (-5 to +10 min window) after the start of the pembrolizumab infusion (-5 to +10 min window), at the end of the pembrolizumab infusion (-5 to + 10 min window) and at 30 min (± 10 min) after completion of the pembrolizumab infusion for participants in the combination therapy.

f. Obtain predose on dosing days.

g. If chest X-ray is performed prior to 2 weeks of screening (prior to ICF and performed as part of standard of care), then it does not need to be repeated.

h. During ASP7517 and pembrolizumab combination therapy, 12-lead ECGs will be recorded in triplicate (at least 2 min apart per time point) and transmitted electronically for central reading. After treatment with ASP7517 has been discontinued, 12-lead ECGs will be recorded as a single assessment (in triplicate if deemed necessary, at least 2 min apart per time point) and read locally. ECG may be repeated once during screening. On IP administration days, ECGs will be obtained:

- At C1D1 and any visit when pembrolizumab and ASP7517 are administered together, ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of ASP7517.
- ASP7517 dosing only: ECGs are obtained predose (-1 h from start of ASP7517 infusion) and 1 to 2 h post dose of ASP7517.
- Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.

i. Includes medications taken within 28 days prior to C1D1. Include all anticancer treatment received 28 days prior to IP administration.

j. Urine or serum pregnancy test will be performed in WOCBP. On treatment visit days, test must occur prior to IP administration.

k. Laboratory tests will be analyzed by the institution's local laboratory. However, sample results must also be submitted for centralized data entry. Laboratory test may be repeated during the screening period.

l. Thyroid panel including triiodothyronine or free triiodothyronine, free thyroxine and thyroid stimulating hormone will be measured prior to receiving pembrolizumab only for participants in the combination cohort. If the thyroid panel is to be measured on same day of pembrolizumab dosing (ex. C4D1, pembrolizumab monotherapy dosing visit), the thyroid panel must be measured prior to receiving pembrolizumab. Thyroid panels assessed on C1D1 and C2D15 only apply for the combination therapy cohort.

m. Whole blood for optional PGx study may be collected at C1D1 prior to IP administration.

n. See Table 6 for collection schedule for ASP7517 monotherapy and ASP7517 and pembrolizumab combination therapy.

o. Archival tumor specimen at a minimum of 1 FFPE tumor tissue block with adequate viable tumor cells (preferred) OR a minimum of 20 FFPE unstained serial slides are required.

p. Same technique (CT/MRI) used at screening should be utilized throughout the study. Imaging should include chest, abdomen and pelvis, as well as any other anatomical region appropriate for the participant's disease. Scans performed prior to informed consent as standard of care are acceptable as screening scans, if done within 28 days prior to C1D1.

q. Participants in all expansion cohorts are required to provide a tumor specimen obtained within 56 days prior to first dose of IP.

r. Participants in all expansion cohorts are required to provide an on-treatment tumor specimen collected ± 7 days of the C2D15 visit (or unscheduled) if predose biopsy is available and if medically feasible.

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s. If the participant will discontinue treatment due to meeting protocol criteria of CR after completion of Cycle 4 or a participant completes all 6 cycles of ASP7517, then all visits in the treatment cycle should be completed and the EOT visit will be performed 7 days (+ up to a 7-day window) after the last planned visit.
   - If participant has CR after completing Cycle 4, the EOT visit would be performed between C4D22 and C4D29.
   - If participant has SD or PR after completing Cycle 4, they are expected to complete all visits through C6D15 and the EOT visit would be performed between C6D22 and C6D29.
   - If the investigator decides to discontinue treatment prior to the completion of any cycle, the EOT visit will occur 7 days after the decision to discontinue treatment.
   - If new anticancer therapy is to be initiated, the EOT visit must occur prior to start of the new therapy, even if < 7 days from the decision to discontinue treatment.
   - For combination therapy participants that continue with pembrolizumab monotherapy, EOT visit will be performed 7 days after 17th dose of pembrolizumab or 7 days after decision to discontinue treatment, or prior to start of new anticancer therapy, whichever is earliest.

Table 21 Study Interruption: Schedule of Assessments for Safety Follow-up, Observation Period and Survival Follow-up Period for Participants who End the Treatment Early or Completed the Treatment Period

Visit	Alternate Approach(es)	Observation Period				Survival Follow-up
		Safety Follow-up[f]			Disease Assessment, Up to 48 weeks[a]	
Window (days)		30 days from last dose	60 days from last dose	90 days from last dose	Visits every 8 weeks ±1 week from last planned scan	Every 3 months
		±3	±3	±3		±7
Physical Examination	Can be obtained at local facility and results submitted to PI	X	X	X		
Vital Signs	Exams can be performed at a local clinic per SOC and results submitted to PI for evaluation	X	X	X		
ECOG Performance	Can be completed by phone contact	X	X	X		
Concomitant Medications	Can be completed by phone contact	X	X	X		
12-Lead ECG	Except for IP administration days triplicate may be performed as possible at a local clinic and results submitted to PI. If cannot be performed, Astellas Medical Monitor to assess for study continuation.	X	X	X		
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)	Collection of samples at local facility acceptable if results can be made available to investigative site	X	X	X		
Pregnancy Test for WOCBP	Test may be performed at local clinical and result submitted to PI	X	X	X		
AE/SAE Assessment	Completed by phone contact allowed with further assessment at local clinic if needed	X	X	X		
Pharmacokinetic sample for cell kinetics (ASP7517)	None	See Table 6 for sample time points				
Blood Sample for anti-WT1 antibody	None	X	X	X	X[b]	
Blood Sample for Immune Response Biomarker (ELISpot)	None	X	X	X	X[c]	
Blood Sample for Immune Response Biomarker (Tetramer)	None	X	X	X	X[b]	

Table continued on next page

Footnotes

Visit	**Alternate Approach(es)**	**Observation Period**				**Survival Follow-up**
		Safety Follow-up[f]			**Disease Assessment, Up to 48 weeks[a]**	
Window (days)		30 days from last dose	60 days from last dose	90 days from last dose	Visits every 8 weeks ±1 week from last planned scan	Every 3 months
		±3	±3	±3		±7
Blood Sample for Immune Cell Phenotyping	None	X	X	X	X[c]	
Blood Sample for Cytokines	None	X	X	X	X[c]	
Blood Sample for ctDNA	None	X	X	X	X[d]	
Radiographic Disease Assessment	Assessment to be done per protocol requirements. Outside of the window assessments need to be escalated to Astellas Medical Monitor				X	
Survival Follow-up[e]	Can be completed by phone contact per protocol design.					X

AE: adverse event; ctDNA: circulating tumor DNA; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; EOT: end of treatment; iCPD: "immune" confirmed progressive disease; iUPD: unconfirmed disease progression disease based on iRECIST; SAE: serious adverse event; WOCBP: woman of childbearing potential; WT1: Wilms' tumor 1 protein.

a. For participants in ASP7517 monotherapy treatment arm. Participants in the Observation period will be followed until iCPD, iUPD who are not clinically stable, clinical disease progression, initiation of a new anticancer therapy or for a total of up to 48 weeks starting at EOT, whichever occurs first.

b. Maximum of 5 samples collected during the Observation Period. Sample will be collected at the time of the disease assessment visit.

c. Maximum of 1 sample collected during the Observation Period. Sample will be collected at the time of the disease assessment visit.

d. Sample will be collected only at the time of discontinuation due to disease progression.

e. Outcomes will be assessed by telephone calls every 3 months for up to 12 months.

f. In the Monotherapy Arm, Safety Follow-up is a part of the 48 weeks Observation period. Observation period starts after EOT.

Table 22 Study Interruption: Schedule of Assessments for Observation Period, Safety Follow-up and Survival Follow-up for Participants who Receive Pembrolizumab Monotherapy in the Observation Period

Visit	Alternate Approach(es)	Observation Period Up to 96weeks[a]	Safety Follow-up			Survival Follow-up
		Visits every 6 weeks (±1 week) from last Pembrolizumab dose during combination treatment	30 days from last dose	60 days from last dose	90 days from last dose	Every 3 months
Window (days)			±3	±3	±3	±7
Physical Examination	Can be obtained at local facility and results submitted to PI	X	X	X	X	
Vital Signs	Exams can be performed at a local clinic per SOC and results submitted to PI for evaluation	X[b]	X	X	X	
ECOG Performance	Can be completed by phone contact		X	X	X	
Concomitant Medications	Can be completed by phone contact	X	X	X	X	
12-Lead ECG	Except for IP administration days triplicate may be performed as possible at a local clinic and results submitted to PI. If cannot be performed, Astellas Medical Monitor to assess for study continuation.	X[c]	X	X	X	
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)	Collection of samples at local facility acceptable if results can be made available to investigative site	X[c]	X	X	X	
Thyroid Profile Panel (triiodothyronine or free triiodothyronine, free thyroxine and thyroid stimulating hormone)	Collection of samples at local facility acceptable if results can be made available to investigative site	X[c]	X[c]			
Pregnancy Test for WOCBP	Test may be performed at local clinical and result submitted to PI	X[c]	X	X	X	
AE/SAE Assessment	Completed by phone contact allowed with further assessment at local clinic if needed	X	X	X	X	
Pharmacokinetic samples for cell kinetics (ASP7517)	None	See Table 6 in the Protocol for schedule				
Pharmacokinetic sample for pembrolizumab	None	See Table 6 in the Protocol for schedule				
Blood Sample for anti-WT1 antibody	None	X[c,h]				

Table continued on next page

Footnotes

Visit	Alternate Approach(es)	Observation Period Up to 96weeks[a]	Safety Follow-up			Survival Follow-up
		Visits every 6 weeks (±1 week) from last Pembrolizumab dose during combination treatment	30 days from last dose	60 days from last dose	90 days from last dose	Every 3 months
Window (days)			±3	±3	±3	±7
Blood Sample for Immune Response Biomarker (ELISpot)	None	X[c,g]				
Blood Sample for Immune Response Biomarker (Tetramer)	None	X[c,h]				
Blood Sample for Immune Cell Phenotyping	None	X[c,g]				
Blood Sample for Cytokines	None	X[c,g]				
Blood Sample for ctDNA	None	X[c,f]				
Radiographic Disease Assessment	Assessment to be done per protocol requirements. Outside of the window assessments need to be escalated to Astellas Medical Monitor	X[d]				
Pembrolizumab Dosing	Assessment to be done per protocol requirements. Outside of the window assessments need to be escalated to Astellas Medical Monitor	X[e]				
Survival Follow-up[i]	Can be completed by phone contact per protocol design.					X

AE: adverse event; C5D15: Cycle 5 Day 15; CR: complete response; ctDNA: circulating tumor DNA; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ELISpot: enzyme-linked immunospot; iCPD: "immune" confirmed progressive disease; iUPD: unconfirmed disease progression disease based on iRECIST; PR: partial response; SAE: serious adverse event; SD: stable disease: WOCBP: woman of childbearing potential; WT1: Wilms' tumor 1 protein.

a. For participants in ASP7517 and pembrolizumab treatment who have achieved CR, PR or SD and receiving pembrolizumab monotherapy. Pembrolizumab will be administered every 6 weeks for up to a total of 17 doses. Participants in the Observation period will be followed until iCPD, iUPD who are not clinically stable, clinical disease progression, initiation of a new anticancer therapy or for a total of up to 78 weeks, whichever occurs first. If participant discontinues combination treatment of ASP7517 at any time prior to C5D15, then the participant should continue observation period up to 96 weeks.
b. Vital signs should be obtained prior to pembrolizumab infusion and within 30 min (± 10 min window) after completion of pembrolizumab infusion.
c. Obtained predose.
d. Disease assessment every 8 weeks.
e. Pembrolizumab administered every 6 weeks for up to 17 doses total (for the study) for those participants who, in the opinion of the investigator, are continuing to derive clinical benefit.
f. Sample collected at the time of discontinuation due to disease progression.
g. Sample collected at the time of pembrolizumab administration of doses 5 and 7.

Footnotes continued on next page

h. Sample collected at the time of pembrolizumab administration of doses 5, 7, 9, 11 and 13.
i. Outcomes will be assessed by telephone calls every 3 months for up to 12 months, starting from the 90-day safety follow-up or last visit prior to the start of new anti-cancer therapy.

Table 23 Study Interruption: Schedule of Replication Competent Lentivirus for Dose Escalation Cohort and Dose Expansion Cohort

Assessment	Alternate Approach(es)	C1D1	3 Months After Treatment Initiation or at End of Treatment, Whichever is First	6 Months after Treatment Initiation	12 Months after Treatment Initiation	18 Months after Treatment Initiation
Window		0	±7 days	±1 month	±1 month	+1 month
Blood Sample for RCL[a]	None: to collect at the first time participant is able to come to the clinic	X[b]	X	X	X	X

C1D1: Cycle 1 Day 1; RCL: replication competent lentivirus

a. If there are positive results, additional follow-up assessments may be required. Refer to [Section 7.7.1].

b. Obtained predose.

INVESTIGATIONAL MEDICINAL PRODUCT SUPPLY

If any of the conditions outlined above in the Participants Procedures Assessment are met, the following mitigating strategies will be employed, as needed, to ensure continuity of IMP supply to the participants:

- Increase stock of IMP on site to reduce number of shipments required, if site storage condition will allow, however each shipment will be closely monitored by Astellas.

DATA COLLECTION REQUIREMENTS

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window, or other modifications) due to the crisis.

10.13 List of Abbreviations and Definition of Key Study Terms

List of Abbreviations

Abbreviations	Description of abbreviations
aAVC	artificial adjuvant vector cell
ADL	activities of daily living
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-PD-1	anti-programmed cell death protein 1
AST	aspartate aminotransferase
AT	aminotransferases
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{last}	area under the concentration-time curve from the time of dosing up to the time of the last measurable concentration
AUC_{28d}	area under the concentration-time curve from time zero to Day 28
BOIN	Bayesian optimal interval
BOP2	Bayesian optimal phase 2
C1D1	Cycle 1 Day 1
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum concentration
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRC	colorectal cancer
CRO	contract research organization
CRS	cytokine-release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	common terminology criteria for adverse events
ctDNA	circulating tumor DNA
C_{trough}	concentration immediately prior to dosing at multiple dosing
DCR	disease control rate per RECIST v1.1
DESC	Dose Escalation and Safety Committee
DLT	dose limiting toxicity
DOR	duration of response per RECIST v1.1
DPD	Data Protection Directive
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviations	Description of abbreviations
eCRF	electronic case report form
eGFR	epidermal growth factor receptor
ELISpot	enzyme-linked immunospot
EOT	end of treatment
FAS	full analysis set
FFPE	formalin-fixed, paraffin embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HLA	human leukocyte antigen
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	"immune" confirmed progressive disease
iCR	complete response based on iRECIST
iDCR	disease control rate per iRECIST
iDOR	duration of response per iRECIST
IEC	Independent Ethics Committee
IFNγ	interferon gamma
IMP	investigational medicinal product
INR	international normalized ratio
iORR	objective response rate per iRECIST
IP	investigational product
iPFS	progression-free survival per iRECIST
iPR	partial response based on iRECIST
irAE	immune-related AE
IRB	Institutional Review Board
iRECIST	immune response evaluation criteria in solid tumors
IRR	infusion-related reactions
IRT	interactive response technology
iSD	stable disease per iRECIST
ISN	international study number
iUPD	unconfirmed disease progression disease based on iRECIST
LA-CRF	liver abnormality case report form
LFT	liver function test
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NK	natural killer

Abbreviations	Description of abbreviations
NKT	natural killer T
ORR	objective response rate per RECIST v1.1
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand
PFS	progression-free survival per RECIST v1.1
PGx	pharmacogenomic
PI	principal investigator
PKAS	pharmacokinetic analysis set
PMDA	Pharmaceutical and Medical Devices Agency
po	by mouth
PR	partial response
PT/INR	prothrombin time/international normalized ratio
PV	pharmacovigilance
QA	quality assurance
QC	quality control
QTL	quality tolerance limit
RAS	response analysis set
RCL	replication competent lentivirus
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
(S)AE	serious adverse event or adverse event
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	stable disease
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
t_{max}	time of maximum concentration
ULN	upper limit of normal
WOCBP	woman of childbearing potential
WT1	Wilms' tumor protein 1

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	Assessments of participants as they enter a study before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study. Note: Not all endpoints are themselves assessments since certain endpoints might apply to populations or emerge from analysis of results. That is, endpoints might be facts about assessments (e.g., prolongation of survival).
Enroll	To register or enter a participant into a study. Note: Once a participant has received the IP or placebo, the protocol applies to the participant.
Investigational Product	The drug, device, therapy or process under investigation in a study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test product or comparative drug (sometimes without randomization) is given to a participant, and continues until the last assessment after completing administration of the test product or comparative drug.
Randomization	The process of assigning participants to treatment or control groups using an element of chance to determine assignments in order to reduce bias. NOTE: Unequal randomization is used to allocate participants into groups at a differential rate; for example, 3 participants may be assigned to a treatment group for every one assigned to the control group.
Screening	A process of active consideration of potential participants for randomization in a study.
Screen failure	Potential participant who signed the ICF, but did not meet one or more criteria required for participation in the study and was not randomized.
Screening period	Period of time before entering the investigational period, usually from the time when a participant signs the consent form until just before the test product or comparative drug (sometimes without randomization) is given to a participant.
Study period	Period of time from the first study site initiation date to the last study site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

11 REFERENCES

Adams M, Calvert AH, Carmichael J, Clark PI, Coleman RE, Earl HM, et al. Chemotherapy for ovarian cancer – a consensus statement on standard practice. Br J Cancer. 1998;78:1404-6.

American Cancer Society. Cancer Facts and Figures 2020. American Cancer Society, Atlanta, GA 2020. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf. Accessed 04 Aug 2020.

Bejrananda T, Phukaoloun M, Boonpipattanapong T, Wanitsuwan W, Kanngern S, Sangthong R, et al. WT1 expression as an independent marker of poor prognosis in colorectal cancers. Cancer Biomark. 2010;8:35-42.

Canadian Agency for Drugs and Technologies in Health. CADTH technology review: optimal use 360 report: dosing and timing of immuno-oncology drugs. Published online November 2019. Available at: https://www.cadth.ca/sites/default/files/ou-tr/ho0008-dosing-timing-immuno-oncology-drugs.pdf. Accessed 19 May 2020.

Cheever MA, Allison JP, Ferris AS, Finn OJ, Hastings BM, Hecht TT, et al. The prioritization of cancer antigens: a national cancer institute pilot project for the acceleration of translational research. Clin Cancer Res. 2009;15:5323-37.

Christensen TD, Jensen SG, Larsen FO, Nielsen DL. Systematic review: Incidence, risk factors, survival and treatment of bone metastases from colorectal cancer. J Bone Oncol. 2018;13:97-105.

Dao T, Yan S, Veomett N, Pankov D, Zhou L, Korontsvit T, et al. Targeting the intracellular WT1 oncogene product with a therapeutic human antibody. Sci Transl Med. 2013;5:176ra33.

Doubeni CA, Doubeni AR, Myers AE. Diagnosis and management of ovarian cancer. Am Fam Physician. 2016;93:937-44.

Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3:524-48.

Gessler M, Poustka A, Cavenee W, Neve RL, Orkin SH, Bruns GA. Homozygous deletion in Wilms tumours of a zinc-finger gene identified by chromosome jumping. Nature. 1990;343:774-8.

Goldstein DA, Gordon N, Davidescu M, Leshno M, Steuer CE, Patel N, et al. A pharmacoeconomic analysis of personalized dosing vs fixed dosing of pembrolizumab in firstline PD-L1-positive non-small cell lung cancer. J Natl Cancer Inst. 2017;109(11).

Ishikawa A, Motohashi S, Ishikawa E, Fuchida H, Higashino K, Otsuji M, et al. A phase I study of α galactosylceramide (KRN7000)-pulsed dendritic cells in patients with advanced and recurrent non-small cell lung cancer. Clin Cancer Res. 2005;11:1910-7.

Keilholz U, Letsch A, Busse A, Asemissen AM, Bauer S, Blau IW, et al. A clinical and immunologic phase 2 trial of Wilms tumor gene product 1 (WT1) peptide vaccination in patients with AML and MDS. Blood. 2009;113:6541-8.

KEYTRUDA (pembrolizumab) injection, for intravenous use (prescribing information). Whitehouse Station, NJ: Merck & Co., Inc.; June 2020.

Köbel M, Kalloger SE, Boyd N, McKinney S, Mehl E, Palmer C, et al. Ovarian carcinoma subtypes are different diseases: implications for biomarker studies. PLoS Med. 2008;5:e232.

Kunii N, Horiguchi S, Motohashi S, Yamamoto H, Ueno N, Yamamoto S, et al. Combination therapy of in vitro-expanded natural killer T cells and α galactosylceramide-pulsed antigen-presenting cells in patients with recurrent head and neck carcinoma. Cancer Sci. 2009;100:1092-8.

Lala M, Li M, Sinha V, de Alwis D, Chartash E, Jain L. A six-weekly (Q6W) dosing schedule for pembrolizumab based on an exposure-response (E-R) evaluation using modeling and simulation. J Clin Oncol. 2018;36:3062.

Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124:188-95.

Liu S and Yuan Y. Bayesian optimal interval designs for phase I clinical trials. J R Stat Soc Ser C Appl Stat. 2015;64:507-23.

Luke JJ, Flaherty KT, Ribas A, Long GV. Targeted agents and immunotherapies: optimizing outcomes in melanoma. Nat Rev Clin Oncol. 2017;14:463-82.

Maslak PG, Dao T, Bernal Y, Chanel SM, Zhang R, Frattini M, et al. Phase 2 trial of a multivalent WT1 peptide vaccine (galinpepimut-S) in acute myeloid leukemia. Blood Adv. 2018;2:224-34

Matsuo K, Lin YG, Roman LD, Sood AK. Overcoming platinum resistance in ovarian carcinoma. Expert Opin Investig Drugs. 2010;19:1339-54.

Menssen HD, Bertelmann E, Bartelt S, Schmidt RA, Pecher G, Schramm K, et al. Wilms' tumor gene (WT1) expression in lung cancer, colon cancer and glioblastoma cell lines compared to freshly isolated tumor specimens. J Cancer Res Clin Oncol 2000;126:226-32.

Miwa H, Beran M, Saunders GF. Expression of the Wilms' tumor gene (WT1) in human leukemias. Leukemia. 1992;6:405-9.

Miyoshi Y, Ando A, Egawa C, Taguchi T, Tamaki Y, Tamaki H, et al. High expression of Wilms' tumor suppressor gene predicts poor prognosis in breast cancer patients. Clin Cancer Res. 2002;8:1167-71.

Motohashi S, Nagato K, Kunii N, Yamamoto H, Yamasaki K, Okita K, et al. A phase I-II study of α glactosylceramide-pulsed IL-2/GM-CSF-cultured peripheral blood mononuclear cells in patients with advanced and recurrent non-small cell lung cancer. J Immunol. 2009;182:2492-501.

Nakatsuka S, Oji Y, Horiuchi T, Kanda T, Kitagawa M, Takeuchi T, et al. Immunohistochemical detection of WT1protein in a variety of cancer cells. Mod Pathol. 2006;19:804-14.

Oji Y, Ogawa H, Tamaki H, Oka Y, Tsuboi A, Kim EH, et al. Expression of the Wilms' tumor gene WT1 in solid tumors and its involvement in tumor cell growth. Jpn J Cancer Res. 1999;90:194-204.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Ozols RF. Treatment of recurrent ovarian cancer: increasing options -- "recurrent" results. J Clin Oncol. 1997;15:2177–80.

Qi X, Zhang F, Wu H, Liu J, Zong B, Xu C, et al. Wilms' tumor 1 (WT1) expression and prognosis in solid cancer patients: a systematic review and meta-analysis. Sci Rep. 2015;5:8924. Available at: https://www.nature.com/articles/srep08924. Accessed 04 Aug 2020.

Shimokawa M, Kogawa T, Shimada T, Saito T, Kumagai H, Ohki M, et al. Overall survival and post-progression survival are potent endpoint in phase III trials of second/third-line chemotherapy for advanced or recurrent epithelial ovarian cancer. J Cancer. 2018;9:872-9.

Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin. 2014;64:104-17.

Simeone E, Ascierto PA. Anti-PD-1 and PD-L1 antibodies in metastatic melanoma. Melanoma Manag. 2017;4:175-8.

Sotobori T, Udea T, Oji Y, Naka N, Araki N, Myoui A, et al. Prognostic significance of Wilms tumor gene (WT1) mRNA expression in soft tissue sarcoma. Cancer. 2006;106:2233-40.

Sugiyama H. WT1 (Wilms' Tumor Gene 1): Biology and Cancer Immunotherapy. Jpn J Clin Oncol. 2010;40(5)377–87.

Sugiyama H. Wilms' tumor gene WT1: its oncogenic function and clinical application. Int J Hematol. 2001;73:177-87.

Temple R. Hy's Law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15(4):241-3.

Uchida T, Horiguchi S, Tanaka Y, Yamamoto H, Kunii N, Motohashi S, et al. Phase I study of α galactosylceramide-pulsed antigen presenting cells administration to the nasal submucosa in unresectable or recurrent head and neck cancer. Cancer Immunol Immunother. 2008;57:337-45.

Wagner N, Panelos J, Massi D, Wagner KD. The Wilms' tumor suppressor WT1 is associated with melanoma proliferation. Pfugers Arch - Eur J Physiol. 2008;455:839-47.

Weeks JC, Catalano PJ, Cronin A, Finkelman MD, Mack JW, Keating NK, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med. 2012;367:1616-25.

Zacharakis M, Xynos ID, Lazaris A, Smaro T, Kosma C, Dokou A, et al. Predictors of survival in stage IV metastatic colorectal cancer. Anticancer Res. 2010;30:653-60.

Zhou H, Lee JJ, Yuan Y. BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints. Stat Med. 2017;36(21):3302-14.

12 ATTACHMENT 1: PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol 7517-CL-1101 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

Substantial Amendment 6, 10 Feb 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The purpose of this amendment is to clarify that the patient population in the monotherapy arm of the dose expansion cohort will include Japanese participants.

Summary of Changes

Table 1 Substantial Changes

Section Number	Description of Change	Brief Rationale
1.1, 4.1.6.2 and 6.3.1	Clarify that Japanese participants will enroll in the monotherapy arm of the dose expansion cohort.	To clarify that the patient population in the monotherapy arm of the dose expansion cohort will include Japanese participants
5.1	Revise inclusion criterion 1 for Additional Inclusion Criteria for Participants in the Expansion Cohorts	To clarify a target population for ASP7517 monotherapy
7.8	Updated total amount of blood collectioned	

Table 2 Nonsubstantial Changes

Section Number	Description of Change	Brief Rationale
1.1, 1.2, 1.3, 4.1.1, 4.1.3, 10.12	Update the maximum pembrolizumab treatment to up to an additional 17 doses	This revision is made for clarification in the event that participants in the combination therapy cohorts discontinue ASP7517 treatment early.
1.3 (Tables 1 and 2), 10.12 (Tables 19 and 20)	Add Thyroid Profile Panel assessments on C1D1 and C2D15 (for combination therapy cohorts)	Accounts for thyroid monitoring required for pembrolizumab administration
1.3 (Tables 1 and 2), 10.12 (Tables 19 and 20)	Update 12-lead ECG footnotes to clarify timing of ECG monitoring when ASP7517 and pembrolizumab are administered together or separately	This revision is made for clarification.
7.5.2	Add that a participant with both an FFPE block and a frozen tissue specimen taken within 56 days prior to the first dose of study treatment does not need to provide a new biopsy	This revision is made for clarification.
10.6	Remove blast count and cell count from Table 14	This parameter is not applicable to this study.
10.6	Add a footnote to clarify testing for HCO3	This revision is made for clarification.
10.8, 10.11	Remove no subsequent dosing from premedication at subsequent dosing for Grades 3 or 4 in Tables 15 and 18	This revision is made for clarification.
Throughout	Minor administrative-type changes (e.g., typos, format, numbering and consistency throughout the protocol) and change *subject* and *patient* to *participant* throughout	To provide clarifications to the protocol and to ensure complete understanding of study procedures.

13 SPONSOR SIGNATURE

Astellas Signatories

(Electronic signatures are attached at the end of the document.)

PPD

Medical Science

PPD

Data Science