A Phase 1/2 Open-label Study Investigating the Safety, Tolerability and Efficacy of ASP0739 as a Single Agent and in Combination with Pembrolizumab in Patients with Advanced Solid Tumors known to Express NY-ESO-1

ISN/Protocol 0739-CL-0101

Version 5.0

Incorporating Substantial Amendment 4 [See Section 12]

24 Aug 2022

IND 26983

IND Grantor: CBER

Sponsor:

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

Protocol History:
Version 1.0 [06 Nov 2020]
Version 2.0 Incorporating Substantial Amendment 1 [01 Feb 2021]
Version 3.0 Incorporating Substantial Amendment 2 [01 Jul 2021]
Version 4.0 Incorporating Substantial Amendment 3 [04 Jan 2022]

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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

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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** **International fax number: +44-800-471-5263** **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. (APGD) 1 Astellas Way, Northbrook, Illinois 60062 USA *PPD*

1 PROTOCOL SUMMARY

1.1 Synopsis

Title of Study:
A Phase 1/2 Open-label Study Investigating the Safety, Tolerability and Efficacy of ASP0739 as a Single Agent and in Combination with Pembrolizumab in Patients with Advanced Solid Tumors known to Express NY-ESO-1

Planned Study Period/Duration:
From approximately 2Q2021 to 2Q2025

Planned Total Number of Study Sites and Location(s):
Approximately 30 study sites
North America and Japan

Study Objectives and Endpoints:

Objective(s)	Endpoint(s)
Primary	
● To evaluate the safety and tolerability of ASP0739 in participants with R/R solid tumors known to express NY-ESO-1 when administered as a single agent (phase 1 dose escalation), and in combination with pembrolizumab in participants with R/R SS, MRCL and ovarian cancer (safety lead-in)	● Safety and tolerability as noted by: DLTs, AEs, SAEs, laboratory test results (serum chemistry, hematology, coagulation, urinalysis, and pregnancy test), ECGs, vital signs, physical exams and ECOG performance status scores
● To determine RP2D of ASP0739 when administered as a single agent	● RP2D based on above
● To evaluate the clinical response of ASP0739 when administered as a single agent and in combination with pembrolizumab in participants with R/R SS, MRCL and ovarian cancer (phase 2)	● Objective response rate per iRECIST (iORR) by Independent Central Review
Secondary	
● To evaluate other measures of anticancer activity of ASP0739 when administered as a single agent and in combination with pembrolizumab based on central and local assessment in participants with R/R SS, MRCL or ovarian cancer (phase 2)	● 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)

Table continued on next page

Objective(s)	**Endpoint(s)**
Secondary *(continued)*	
• To obtain preliminary efficacy based on central and local assessment in participants with R/R solid tumors known to express NY-ESO-1 (melanoma, NSCLC-adenocarcinoma and squamous cell and ESCC) (phase 2)	• Objective response rate per iRECIST (iORR)
Exploratory	
• To evaluate potential genomic, proteomic and/or other biomarkers that may correlate with treatment outcome when ASP0739 is administered as a single agent and in combination with pembrolizumab	• Exploratory biomarkers that may correlate with treatment outcome of ASP0739 as a single agent or in combination with pembrolizumab, including NY-ESO-1 expression
• To evaluate pharmacodynamic activities of ASP0739 as a single agent and in combination with pembrolizumab	• Pharmacodynamic effects of ASP0739, such as changes in: o Cytokine expression and secretion (e.g., IFNg) o NY-ESO-1-specific T lymphocytes (e.g., cytotoxic T lymphocytes) o Immune cell populations (NKT cells, Treg cells, etc.) o Anti-NY-ESO-1 antibodies o Tumor microenvironment (CD8, PD-L1, etc.)
• To evaluate pharmacokinetics of ASP0739 when administered as a single agent and in combination with pembrolizumab	• Cellular DNA load and kinetic parameter estimates (including AUC, C_{max}, C_{trough} and t_{max}) for ASP0739 as a single agent or in combination with pembrolizumab

AE: adverse event; CD8: cluster of differentiation 8; DCR: disease control per RECIST v1.1; DLT: dose limiting toxicity; DOR: duration of response per RECIST v1.1; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ESCC: esophageal squamous cell carcinoma; iDCR: disease control per iRECIST; iDOR: duration of response per iRECIST; IFNg; interferon gamma; iORR: objective response rate per iRECIST; iPFS: progression-free survival per iRECIST; iRECIST: immune response evaluation criteria in solid tumors; MRCL: myxoid/round cell liposarcoma; NKT: natural killer T; NSCLC: non-small cell lung cancer; NY-ESO-1: New York esophageal squamous cell carcinoma 1; ORR: objective response rate per RECIST v1.1; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival per RECIST v1.1; R/R: relapsed/refractory; RECIST: response evaluation criteria in solid tumors; RP2D: recommended phase 2 dose; SAE: serious adverse event; SS: synovial sarcoma

Study Population:

Phase 1 (Dose Escalation)

Adult participants with solid tumors relapsed/refractory (R/R) to standard of care (SOC) and known to express New York esophageal squamous cell carcinoma 1 (NY-ESO-1).

Phase 2

Adult participants with synovial sarcoma (SS), myxoid/round cell liposarcoma (MRCL) or ovarian cancer R/R to SOC who have not received prior checkpoint inhibitor therapy will receive ASP0739 as single agent and in combination with pembrolizumab (after a lead-in safety evaluation).

Adult participants with R/R solid tumors known to express NY-ESO-1 (melanoma, non-small cell lung cancer [NSCLC]-adenocarcinoma and squamous cell, and esophageal squamous cell carcinoma [ESCC]) will receive ASP0739 as single agent.

Number of Participants:

A total of approximately 339 participants may be enrolled in the study.

ASP0739 Single Agent

A total of approximately 181 participants may be enrolled in single agent treatment.

Phase 1 (Dose Escalation)

Approximately 12 participants with R/R solid tumors known to express NY-ESO-1.

Phase 2

Approximately 43 participants with R/R SS, 43 participants with R/R MRCL and 43 participants with R/R ovarian cancer will be enrolled once phase 1 single agent dose escalation is completed and the recommended phase 2 dose (RP2D) is defined.

In a separate cohort, approximately 40 participants with R/R solid tumors known to express NY-ESO-1 (melanoma, NSCLC-adenocarcinoma and squamous cell and ESCC) will be enrolled for preliminary efficacy assessment.

ASP0739 Combination with Pembrolizumab

A total of approximately 158 participants may be enrolled in combination therapy.

Safety Lead-in: Enrollment will start upon completion of phase 1 single agent dose escalation and confirmation of RP2D. Approximately 6 to 9 participants with R/R SS, MRCL or ovarian cancer may be enrolled to assess the safety of combination therapy prior to enrolling the specified number of participants for efficacy evaluation in each tumor type that is opened.

Phase 2: Approximately 60 participants with R/R SS, 60 participants with R/R MRCL and 29 participants with R/R ovarian cancer may be enrolled in a same cancer type cohort where 2 local or central radiographic responses (complete response per iRECIST [iCR] or partial response per iRECIST [iPR]) were observed with single agent and the safety lead-in is completed. Groups of participants will enroll in parallel and independently in each cohort.

Study Design Overview:

This is a phase 1, open-label study of ASP0739 in participants with R/R solid tumors known to express NY-ESO-1 and a phase 2 study of single agent and combination therapy with pembrolizumab in participants with R/R SS, MRCL or ovarian cancer.

Phase 1 (dose escalation) in participants with solid tumors known to express NY-ESO-1 and phase 2 of ASP0739 single agent and combination therapy with pembrolizumab in R/R SS, MRCL and ovarian cancer who have not responded to SOC or are ineligible for standard therapy.

Phase 2 single agent will also include a cohort of participants with select solid tumors known to express NY-ESO-1 (melanoma, NSCLC-adenocarcinoma and squamous cell and ESCC).

Both study phases consist of the following periods:

- Screening (up to 28 days)
- Treatment with ASP0739 (up to 6 doses every 28-days) and for participants in combination cohorts with pembrolizumab on cycle 1 day 1 (C1D1), and then every 6 weeks, until disease progression, unacceptable toxicity or up to 17 doses
- EOT visit after completion of investigational product (IP): Within 7 days of EOT determination or prior to the initiation of new anticancer therapy, whichever occurs first
- Safety follow-up visits at 30, 60 and 90 days from the last dose of treatment or prior to the initiation of new anticancer therapy
- Follow-up visits every 2 months for up to 1 year or until progression or start of a new anticancer therapy or death (whichever occurs first)
- Survival follow-up for up to 1 year by telephone calls every 3 months after the start of a new anticancer treatment or progression after ASP0739 and/or pembrolizumab treatment

ASP0739 Single Agent

Participants will receive an intravenous infusion of ASP0739 (human embryonic kidney cells [HEK293] transfected with a lentiviral vector that is encoding the target antigen NY-ESO-1). Participants will receive 1 dose every 28-day cycle for up to 4 doses; an additional 2 doses may be administered in participants with PR or stable disease (SD). Following the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit may continue further treatment with ASP0739, as decided by the investigator.

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

Dose Levels (Phase 1 dose escalation)

Dose Level	Dose
0	1×10^7 cells/dose
+1	1×10^8 cells/dose

ASP0739 Combination with Pembrolizumab

The RP2D of ASP0739 determined from the phase 1 dose escalation phase will be combined with pembrolizumab 400 mg for the safety lead-in with approximately 6 to 9 participants. If the RP2D is selected at the same dose level as the maximum tolerated dose (MTD) based on the phase 1 dose escalation portion, the combination safety lead-in will start at one dose level lower than the MTD.

Participants will receive 1 dose of ASP0739 every 28-day cycle for a total of 4 doses; an additional 2 doses may be administered for participants with PR or SD. Following the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit may continue further treatment with ASP0739 and pembrolizumab, as decided by the investigator. Participants will also receive pembrolizumab 400 mg on C1D1, then every 6 weeks, until disease progression, unacceptable toxicity or for up to a total of 17 doses or until one of the discontinuation criteria is met. For combination treatment, a 400 mg pembrolizumab infusion will be administered first, followed by an ASP0739 infusion at least 1 hour after the completion of the pembrolizumab infusion.

Phase 1 Single Agent Dose Escalation:

The single agent dose escalation phase will evaluate escalating dose levels of ASP0739 in approximately 3 to 12 DLT-evaluable participants.

The dose escalation phase will assess safety and tolerability of ASP0739 during cycle 1. Participants will receive up to 6 doses of ASP0739 via intravenous infusion separated by 28 days. Dosing will occur on day 1 of each cycle. After the first dose of ASP0739, participants must be observed for safety for a minimum of 4 hours. If new adverse events (AEs) are observed that are greater than grade 3 during this time, participants should continue to be observed until the AEs are less than grade 3.

Dose escalation will be guided according to the Bayesian Optimal Interval (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 phase will enroll 3 to 4 evaluable participants for the initial assessment of each dose level.

Enrollment in the single agent dose escalation cohorts will be staggered such that there will be a minimum of 28 calendar days between the treatment initiation of the first and second participants and 14 calendar days between the second and the third participant at the same dose level for all escalation cohorts. In the absence of toxicity, additional participants may be treated at a dose level without any formal stagger. An interval of 28 calendar days will separate study treatment initiation of the last patient in a dose cohort from the first participant treatment in sequential dose cohort.

ASP0739 in Combination with Pembrolizumab Safety Lead-in

Enrollment in the combination therapy safety lead-in will start once phase 1 single agent dose escalation is completed and the RP2D is defined.

The combination therapy safety lead-in portion will evaluate the RP2D of ASP0739 with a fixed dose of 400 mg pembrolizumab in 6 to 9 participants with at least 6 DLT-evaluable participants. If the RP2D is selected at the same dose level as the MTD based on the phase 1 dose escalation portion, the combination safety lead-in will start at one dose level lower than the MTD.

Safety lead-in will be guided according to the BOIN design [Liu & Yuan, 2015] to determine if the RP2D of ASP0739 with a fixed dose of 400 mg pembrolizumab is tolerable and based on DLT occurrence after 28 days. After the planned number of evaluable participants has completed the DLT observation period of 28 days for a given dose level, safety for that dose level will be assessed. Safety lead-in will enroll 3 to 4 evaluable participants for the initial assessment of RP2D. A minimum of 6 participants must be enrolled at the dose level used to determine the RP2D.

Enrollment in the safety lead-in cohort will be staggered such that there will be a minimum of 28 calendar days between the treatment initiation of the first and second participants and 14 calendar days between the second and the third participants at the same dose level for the safety lead-in cohort. In the absence of toxicity, additional participants may be treated at a dose level without any formal stagger. An interval of 28 calendar days will separate study treatment initiation of the last patient in a dose cohort from the first participant treatment in sequential dose cohort.

Study Enrollment Interruption:

Study enrollment will be temporarily interrupted 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/Safety Lead-in:

Participants may be replaced in the safety lead-in or dose escalation cohort if:

- Participant is discovered to have enrolled without fully satisfying eligibility criteria
- Participant did not receive 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

Recommended Phase 2 Dose

The sponsor, in conjunction with the DESC, will determine the RP2D of ASP0739 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 ASP0739.

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

Dose Escalation 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 for the phase 1 dose escalation and phase 2 safety lead-in. 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 expansion and phase 2 expansion cohorts for single agent and combination therapy with pembrolizumab.

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 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 RP2D dose for expansion will not be higher than the MTD. If the RP2D is selected at the same dose level as the MTD based on the phase 1 dose escalation portion, the combination safety lead-in will start at one dose level lower than the MTD.

Phase 2 Single Agent

Once RP2D is determined, the phase 2 single agent cohorts may be opened in R/R SS, MRCL, ovarian cancer and other solid tumors known to express NY-ESO-1 (melanoma, NSCLC-adenocarcinoma and squamous cell and ESCC). If a confirmed response (iPR or iCR, per independent central review or local assessment) occurs in other solid tumors known to express NY-ESO-1, a tumor-specific dose expansion cohort may be opened in that tumor type.

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]. For R/R SS, MRCL and ovarian cancer, initially 18 participants will be enrolled in each tumor-specific expansion cohort (stage 1). If the iORR does not meet the optimal stopping boundaries (see table below), then an additional 25 participants (stage 2) may be enrolled for a total maximum sample

size of 43. When the total number of participants reaches the maximum sample size of 43, it may be predicted that ASP0739 is effective if the number of responses is greater than or equal to 8.

Optimized Stopping Boundaries for SS, MRCL and Ovarian Cancer	
Number of participants treated	**Stop if number of responses ≤**
18	2

MRCL: myxoid/round cell liposarcoma; SS: synovial sarcoma

For the melanoma/NSCLC/ESCC cohort, after a minimum of 10 participants per tumor type are enrolled, if less than approximately 6 participants for each tumor type of melanoma, NSCLC-adenocarcinoma or squamous cell carcinoma or ESCC are NY-ESO-1 positive upon analysis of the most recent tissue sample, then additional participants may be enrolled into the tumor type with less than approximately 6 NY-ESO-1 positive participants.

UNIQUE to Japan Sites:

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

Phase 2 Single Agent Dose Expansion Cohort with Japanese Safety Lead-in

After the phase 1 dose escalation cohort has been completed, the phase 2 single agent dose expansion cohort with Japanese safety lead-in may be opened. The Japanese safety lead-in will enroll 3 to 8 safety evaluable participants to confirm Japanese tolerability of the RP2D of ASP0739. Japanese participants must be managed under hospitalization for 7 days from C1D1 through C1D8 during the Japanese safety lead-in. Prior to hospital discharge, the investigator must ensure participant safety by performing medical tests and procedures listed on Day 8 of Cycle 1. During the Japanese safety lead-in, an interval of 7 days will separate study treatment initiation for the second participant from the first participant. In the absence of toxicity, additional participants may be treated without any formal stagger.

The tolerability of ASP0739 single agent therapy RP2D will be assessed during the DLT observation period, which is from C1D1 to C1D28. Quantitative assessment of DLTs will be performed referring to the concept of a BOIN design with the target DLT rate of 30% and optimal interval of (0.236, 0.359) to determine if the ASP0739 single agent therapy RP2D is tolerable and is based on a DLT occurrence after 28 days. The tolerability evaluation rule is as follows:

	Number of Participants evaluable for DLT Assessment					
	3	**4**	**5**	**6**	**7**	**8**
[Tolerable] If the number of participants with DLTs is equal or less than the number given in the corresponding cell, the ASP0739 single agent therapy RP2D can be determined to be tolerable.	0	0	1	1	1	1
[Stay] If the number of participants with DLTs is equal to the number given in the corresponding cell, enrollment is continued until the maximum number of participants is reached.	1	1	NA	2*	2*	2*
[Not tolerable] If the number of participants with DLTs is equal or greater than the number given in the corresponding cell, the ASP0739 single agent therapy RP2D is determined to be intolerable.	2	2	2	3	3	3

DLT: dose limiting toxicity; NA: not applicable; RP2D: recommended phase 2 dose; TEM: tolerability evaluation meeting

*When the number of participants for DLT assessment reaches the maximum number of participants and the recommended action is Stay, the tolerability of the dose will be assessed comprehensively at the TEM.

A minimum of 3 evaluable participants must be enrolled at the dose level used to determine the tolerability of RP2D in Japanese participants. Three to four safety evaluable participants are enrolled as initial assessment. If the evaluation is to be continued based on DLT occurrence, additional 3 to 4 safety evaluable participants are enrolled. After the tolerability of RP2D is confirmed in Japanese participants, additional Japanese participants may be enrolled into dose expansion part continuously.

Tolerability Evaluation Meeting

A Tolerability Evaluation Meeting (TEM) consisting of sponsor representatives and investigators will convene once the number of Japanese participants (defined in the protocol) completes the DLT observation period and data are available for review. TEM members should consider all available safety findings when making their evaluations and decisions. Additional details regarding responsibilities, membership requirements and safety review time points are included in the TEM Charter.

Replacement of Participants in Japanese Safety Lead-in

Participants may be replaced in the safety lead-in if:

- The participant is discovered to have enrolled without fully satisfying the eligibility criteria.
- The participant received less than the planned dose in C1 for reasons other than a DLT.
- The participant has experienced 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 safety lead-in will not be replaced.

The 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 ASP0739 upon resolution of the DLT event to ≤ grade 1 or baseline.

A participant who meets the stopping criteria will not receive study drug at C2. Additionally, at the TEM, the aggregate safety data are reviewed if any study stopping rules below have been met:

- If a study participant develops a grade 4 DLT after receiving C1
- If a study participant develops a grade ≥ 3 non-hematological AE that does not resolve to ≤ grade 2 within 72 hours of onset

  Note: This event should be considered a DLT.
- If there is a delay in administration of C2 by > 4 weeks, it may result in discontinuation of treatment after discussion with the sponsor.

Study enrollment and study treatment of the Japanese safety lead-in will be temporarily interrupted if any of the following events occur in a participant:

- Any death that is not related to disease progression occurring within 30 days of receiving ASP0739
- Occurrence of 2 grade ≥ 4 DLTs in 2 participants
- Any grade 4 hypersensitivity reaction/anaphylaxis

Phase 2 Combination of ASP0739 + Pembrolizumab

Once safety lead-in is completed and 2 radiographic responses (iCR or iPR) are observed in the phase 2 dose expansion monotherapy cohort by local or central review, the phase 2 combination cohorts may be opened in the respective tumor type where the responses were observed.

For R/R SS, initially 22 participants will be enrolled in an expansion cohort (stage 1). If the iORR does not meet the optimal stopping boundaries (see table below) for R/R SS, then an additional 38 participants (stage 2) may be enrolled for a total maximum sample size of 60. When the total number of participants reaches the maximum sample size of 60, it may be predicted that ASP0739 in combination with pembrolizumab is effective if the number of responses is greater than or equal to 18.

Optimized Stopping Boundaries for SS	
Number of participants treated	**Stop if number of responses ≤**
22	3

SS: synovial sarcoma

For R/R MRCL, initially, 22 participants will be enrolled in an expansion cohort (stage 1). If the iORR does not meet the optimal stopping boundaries (see table below) for R/R MRCL, then an additional 38 participants (stage 2) may be enrolled for a total maximum sample size of 60. When the total number of participants reaches the maximum sample size of 60, it may be predicted that ASP0739 in combination with pembrolizumab is effective if the number of responses is greater than or equal to 18.

Optimized Stopping Boundaries for MRCL	
Number of participants treated	**Stop if number of responses ≤**
22	3

MRCL: myxoid/round cell liposarcoma

For R/R ovarian cancer, initially, 10 participants will be enrolled in an expansion cohort (stage 1). If the iORR does not meet the optimal stopping boundaries (see table below) for R/R ovarian cancer, then an additional 19 participants (stage 2) may be enrolled for a total maximum sample size of 29. When the total number of participants reaches the maximum sample size of 29, it may be predicted that ASP0739 in combination with pembrolizumab is effective if the number of responses is greater than or equal to 4.

Optimized Stopping Boundaries for Ovarian Cancer	
Number of participants treated	**Stop if number of responses ≤**
10	0

If both single agent and combination therapy expansion cohorts are open for the same tumor type, participants will be randomized to either single agent or combination therapy cohorts and the randomization ratio will be based on the number of open slots still available at each cohort.

Replacement of Participants in Phase 2 Dose Expansion

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

Treatment Groups and Duration:

Monotherapy

Arm/IP Name	ASP0739
Use	Test product
Dose	1×10^7 cells/dose, 1×10^8 cells/dose
Frequency	Single dose on day 1 every 4 weeks
Route	Intravenous
Duration	Up to 6 doses

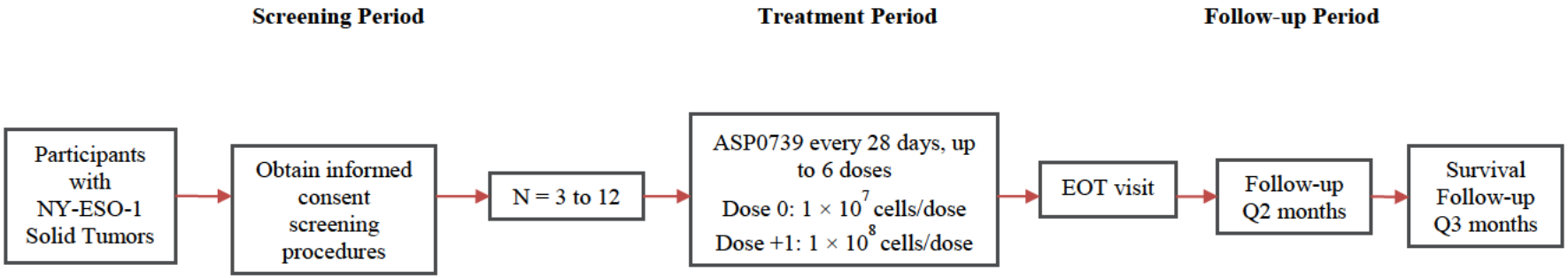
Combination Therapy:

Arm/IP Name	ASP0739 and pembrolizumab
Use	Test product
Dose	1×10^7 cells/dose, 1×10^8 cells/dose (ASP0739); 400 mg (pembrolizumab)
Frequency	ASP0739, single dose on day 1, and then every 4 weeks Pembrolizumab, single dose on day 1, and then every 6 weeks
Route	Intravenous
Duration	Up to 6 doses of ASP0739 in combination with pembrolizumab; with up to 4 doses (pembrolizumab) during the treatment period; a total of 17 doses of pembrolizumab for qualifying participants

1.2 Study Schema

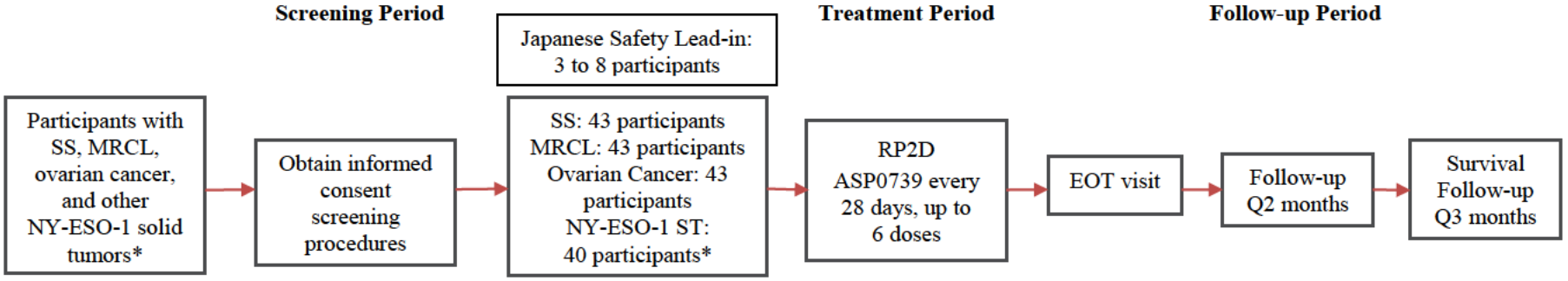
Figure 1 Study Schema

Phase 1 Dose Escalation ASP0739 Single Agent



EOT: end of treatment, NY-ESO-1: New York esophageal squamous cell carcinoma 1; Q; every

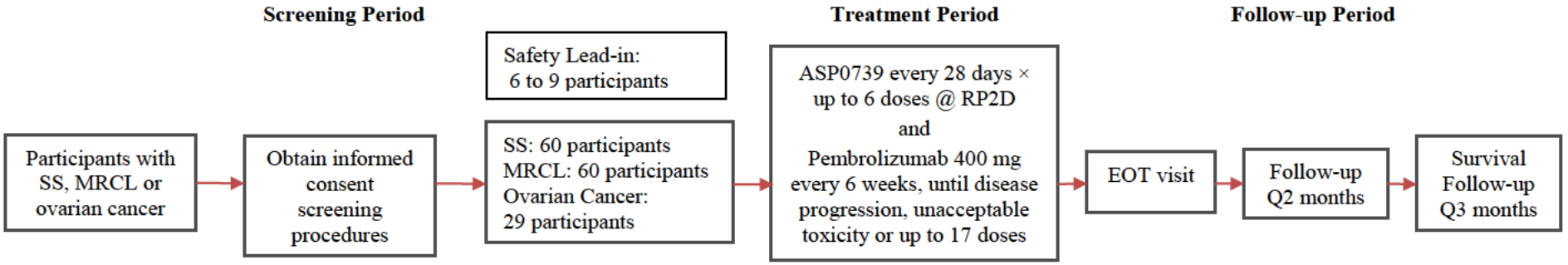
Phase 2 ASP0739 Single Agent



DLT: dose limiting toxicity; EOT: end of treatment; ESCC: esophageal squamous cell carcinoma; MRCL: myxoid/round cell liposarcoma; NSCLC: non-small cell lung cancer; NY-ESO-1: New York esophageal squamous cell carcinoma 1; Q; every; RP2D: recommended phase 2 dose; SS: synovial sarcoma; ST: solid tumor

* Melanoma, NSCLC-adenocarcinoma and squamous cell lung and ESCC (10 participants in each group).

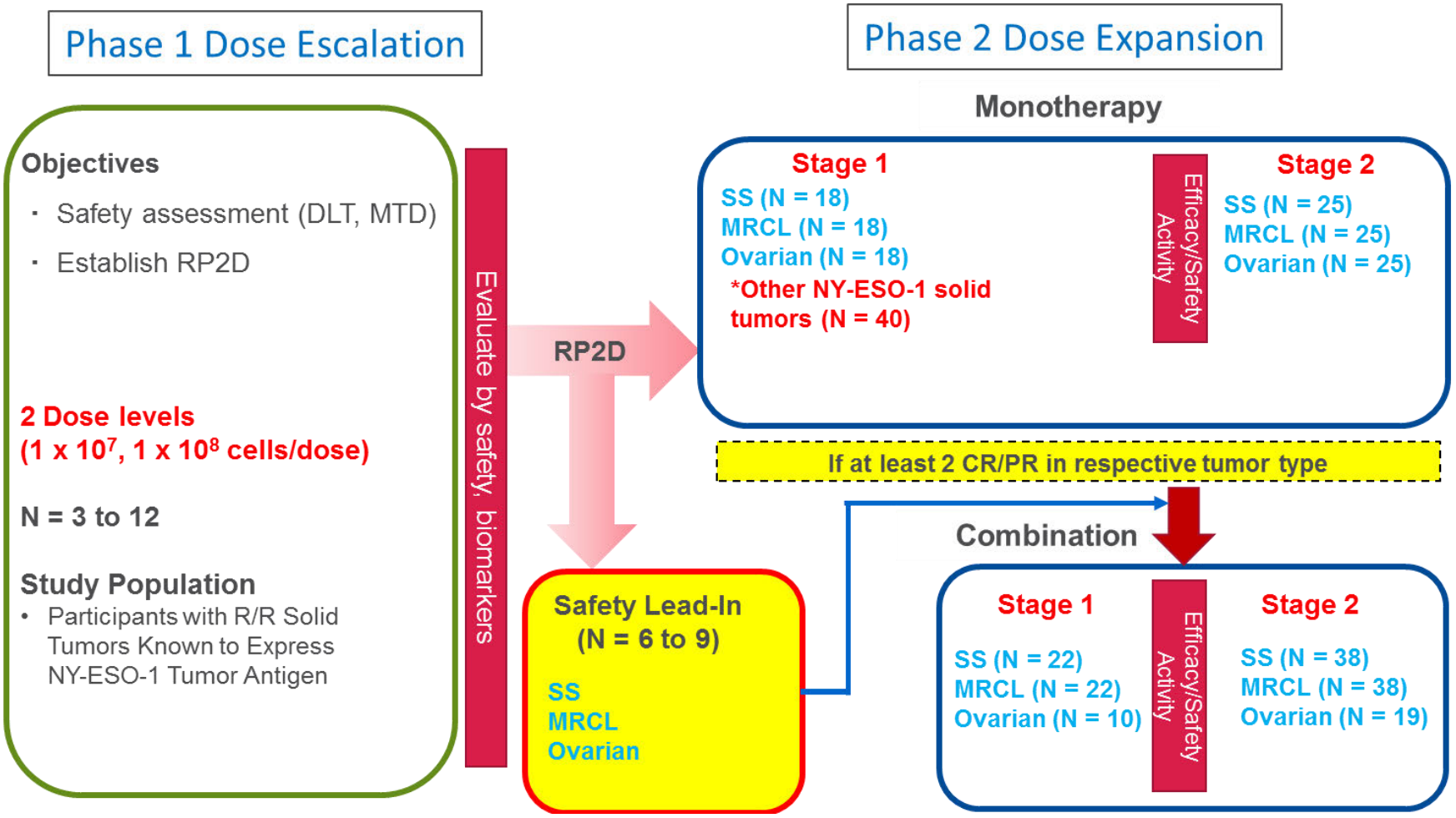
Phase 2 ASP0739 Combination Therapy



EOT: end of treatment, MRCL: myxoid/round cell liposarcoma; MTD: maximum tolerated dose; Q; every; RP2D: recommended phase 2 dose; SS: synovial sarcoma

If the RP2D is selected at the same dose level as the MTD based on the phase 1 dose escalation portion, the combination safety lead-in will start at one dose level lower than the MTD.

Figure 2 Study Design Schema



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CR: complete response per iRECIST; DLT: dose limiting toxicity; ESCC: esophageal squamous cell carcinoma; iRECIST: immune response evaluation criteria in solid tumors; MRCL: myxoid/round cell liposarcoma; MTD: maximum tolerated dose; NSCLC: non-small cell lung cancer; NY-ESO-1: New York esophageal squamous cell carcinoma 1; PR: partial response per iRECIST; RP2D: recommended phase 2 dose; R/R: relapsed/refactory; SS: synovial sarcoma

*Melanoma, NSCLC-adenocarcinoma and squamous cell lung and ESCC.

1.3 Schedules of Assessments

Table 1 Schedule of Assessments – Dose Escalation Cohort and Safety Lead-in Combination Cohort

	Scr	Treatment[a]																				Pembro Mono	EOT[e,y]
		Cycle 1						Cycle 2						Cycles 3–4[b]				Cycles 5–6[c]				Doses 5-17[d]	
Visit Days	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22[y]**	**Every 6 weeks**	
Window (days)			0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	+ 7
Signed ICF	X																						
Medical and Disease History	X																						
Physical Examination[f]	X[f]	X[f]	X		X	X	X	X[f]	X		X	X	X	X[f]	X	X	X	X[f]	X	X	X	X[f]	X[f]
Vital Signs[g]	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance	X	X[h]	X		X	X	X	X[h]	X		X	X[h]	X	X[h]	X	X	X	X[h]	X	X	X	X[h]	X
MUGA or ECHO	X[i]																						
12-Lead ECG[j]	X	X[j]			X	X		X[j]			X	X[j]		X[j]				X[j]					X
Prior and Concomitant Medications	X[k]	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test for WOCBP	X	X[l]						X[l]						X[l]				X[l]				X[l]	X[j]
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[m]	X	X[h]	X		X	X	X	X[h]	X		X	X	X	X[h]	X	X	X	X[h]	X	X	X	X[h]	X
Coagulation Profile (PT/INR, fibrinogen)[m]	X	X[h]	X		X	X	X	X[h]	X		X	X	X	X[h]				X[h]				X[h]	X
Thyroid Profile Panel[m,n]	X											X		Every 6 weeks after C2D15 dose									
PGx[o]		X[o]																					
Buccal Swab for HLA Typing		X[h]																					
AE/SAE Assessment	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Table continued on next page

	Scr	Treatment[a]																				Pembro Mono	EOT[e,y]
		Cycle 1						Cycle 2						Cycles 3–4[b]				Cycles 5–6[c]				Doses 5-17[d]	
Visit Days	**-28 to -1**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22[y]**	**Every 6 weeks**	
Window (days)			0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	+ 7
Pharmacokinetic: ASP0739[p]	See Table 5 for detailed sample time points																						
Pharmacokinetic: Pembrolizumab[p]	See Table 5 for detailed sample time points																						
Anti-NY-ESO-1 antibody		X[h]						X[h]						X[h]				X[h]				X[v]	X
Immune Response Biomarker (ELISpot)		X[h]			X	X		X[h]			X	X		X[h]	X	X		X[h]	X	X		X[v]	X
Immune Response Biomarker (Tetramer)		X[h]				X		X[h]				X		X[h]		X		X[h]		X		X[v]	X
Immune Cell Phenotyping		X[h]			X	X		X[h]			X	X		X[h]	X	X		X[h]	X	X		X[w]	X
Cytokines		X[h]	X	X	X	X		X[h]	X	X	X	X		X[h]	X	X		X[h]	X	X		X[w]	X
Circulating Tumor DNA		X[h]						X[h]						X[h]				X[h]				X	X[x]
Archival Tumor Tissue[q]		X																					
Pulmonary function test[z]	X													X								X	
Radiographic Disease Assessment[r]	X	Every 56 ± 7 days																					
IRT Transaction	X	X[s]						X						X				X				X	
ASP0739 Dosing[t]		X						X						X				X					
Pembrolizumab Dosing[u]		X										X		Every 6 weeks[u]								X	

Footnotes appear on next page

AE: adverse event; C: cycle; CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; ECHO: echocardiogram; 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; MUGA: multiple gated acquisition scan; NY-ESO-1: New York esophageal squamous cell carcinoma 1; Pembro: pembrolizumab; 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

a. Cycles 1 through 6 represent ASP0739 single agent or combination of ASP0739 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 ASP0739 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 ASP0739 in cycles 5 and 6. Participants who reach CR will not receive additional doses of ASP0739.

d. Participants in combination therapy only will continue to receive pembrolizumab as monotherapy for doses 5 up to 17. If participant receives at least 1 dose of ASP0739 but discontinues combination treatment of ASP0739 at any time prior to C5D15, then the participant may continue pembrolizumab as monotherapy for up to 96 weeks for a total of 17 doses of pembrolizumab total for the study.

e. The EOT visit will occur within 7 days of the principal investigator decision to discontinue the participant for treatment or prior to the start of new anticancer treatment, whichever occurs first. If a participant is completing all visits in the last treatment cycle, the EOT visit will be within 7 days from the last planned visit.

f. Height measurement performed at screening only. If height cannot be measured at the screening visit, it can be collected at any time during the course of the study, but should be recorded for the screening visit. Weight measurement performed at screening and day 1 of each cycle.

g. The following vital sign assessments schedules apply:

- At C1D1 and any visit when pembrolizumab and ASP0739 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 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 ASP0739 infusion, every 15 min (-5 to +10 min window) during ASP0739 infusion, at the end of ASP0739 infusion (-5 to +10 min window), and post dose (+30 min, +1, +2, +3 and +4 hours [± 10 min window each] from end of ASP0739 infusion).
- ASP0739 dosing only: vital signs will be obtained within 15 min prior to start of ASP0739 infusion, every 15 min (-5 to +10 min window) during ASP0739 infusion, at the end of ASP0739 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 ASP0739 infusion. If participants are still available, additional optional vital sign assessments 3 hours (± 10 min) and 4 hours (± 10 min) after completion of the ASP0739 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 pembrolizumab infusion; at the end of 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.

h. Obtain predose.

i. If performed within 2 weeks of screening (prior to ICF and performed as part of standard of care), then do not need to be repeated. If participants present positive troponin levels or new onset of cardiovascular symptoms, MUGA or ECHO should be performed.

Footnotes continued on next page

j. 12-lead ECGs will be recorded in triplicate (at least 2 min apart per time point) and transmitted electronically for central reading. On IP administration days, ECG will be obtained:
   - At C1D1 and any visit when pembrolizumab and ASP0739 are administered together, ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of ASP0739.
   - ASP0739 dosing only: ECGs are obtained predose (-1 h from start of ASP0739 infusion) and 1 to 2 h post dose of ASP0739.
   - Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.

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

l. Urine or serum pregnancy test will be performed in women of childbearing potential. On treatment visit days, test must occur prior to IP administration.

m. 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. For participants in combination therapy arm, troponin levels will be obtained at screening; thereafter, weekly for 6 weeks and subsequently every second week for 6 weeks.

n. 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 (Screening, C2D15 then every 6 weeks).

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

p. See Table 5 for collection schedule for ASP0739 single agent and ASP0739 and pembrolizumab combination therapy.

q. 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.

r. 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. Imaging will occur every 56 ± 7 days until confirmed progression by iRECIST.

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

t. In both the monotherapy and combination cohorts, each participant must remain at the site facility for 4 hours following the participant's first dose of ASP0739. For the next dose (second dose) or additional subsequent single agent with ASP0739, participants must remain at the site facility for at least 2 hours after ASP0739 dosing.

u. In the combination therapy arm, pembrolizumab will be administered as an intravenous infusion over 30 min followed by ASP0739 administration at least 1 hour after pembrolizumab administration. For participants enrolled in Japanese safety lead-in, C1D8 assessments should be performed prior to discharge from hospital.

v. Samples collected at pembrolizumab doses 5, 7, 9, 11 and 13 only.

w. Samples collected at pembrolizumab doses 5 and 7 only.

x. Sample collected at the time of discontinuation due to disease progression.

y. If participant is completing all assessments within cycle 6, EOT assessment will be on C6D22 (± 3 days) or prior to the initiation of new anticancer therapy, whichever occurs first.

z. Only participants in the combination therapy arm need to undergo pulmonary function tests at screening and at weeks 12 and 24 of study treatment.

Table 2 Schedule of Assessments for Dose Expansion Monotherapy and Combination Therapy Cohort

	Scr	Treatment[a]																Pembrolizumab Monotherapy	EOT[u,aa]
		Cycle 1						Cycle 2						Cycles 3–4[b]		Cycles 5–6[c]		Doses 5-17[d]	
Visit Days	(-28 to -1)	1	2	4	8	15	22	1	2	4	8	15	22	1	15	1	15	Every 6 weeks	
Window(days)		0	0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	+ 7
Signed ICF	X																		
Medical and Disease History	X																		
Physical Examination[e]	X[e]	X[e]	X	X[bb]	X	X	X	X[e]	X	X[bb]	X	X	X	X[e]	X	X[e]	X	X[e]	X[e]
Vital Signs[f]	X	X	X	X[bb]	X	X	X	X	X	X[bb]	X	X	X	X	X	X	X	X	X
ECOG Performance	X	X[g]	X		X	X	X	X[g]	X		X	X[h]	X	X[g,h]	X[h]	X[g,h]	X[h]	X[g,h]	X
MUGA or ECHO	X[i]																		
12-Lead ECG[j]	X	X[j]						X[j]						X[j]		X[j]			X
Prior and Concomitant Medications	X[k]	X	X	X[bb]	X	X	X	X	X	X[bb]	X	X	X	X	X	X	X	X	X
Pregnancy Test for WOCBP	X	X[l]						X[l]						X[l]		X[l]		X[l]	X
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[m]	X	X[g]	X		X	X	X	X[g]	X		X	X[h]	X	X[g,h]	X[h]	X[g,h]	X[h]	X[g,h]	X
Coagulation Profile (PT/INR, fibrinogen)[m]	X	X[g]	X		X	X	X	X[g]	X		X	X[h]	X	X[g,h]	X[h]	X[g,h]	X[h]	X[g,h]	X
Thyroid Profile Panel[m,n]	X											X		Every 6 weeks after C2D15 dose					X
PGx[o]		X[o]																	
Buccal Swab for HLA Typing		X[g]																	
AE/SAE Assessment	X	X	X	X[bb]	X	X	X	X	X	X[bb]	X	X	X	X	X	X	X	X	X

Table continued on next page

	Scr	Treatment[a]																Pembrolizumab Monotherapy	EOT[u,aa]
		Cycle 1						Cycle 2						Cycles 3–4[b]		Cycles 5–6[c]		Doses 5-17[d]	
Visit Days	(-28 to -1)	1	2	4	8	15	22	1	2	4	8	15	22	1	15	1	15	Every 6 weeks	
Window(days)		0	0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	+ 7
Pharmacokinetic: ASP0739[p]	See Table 5 for sample time points																		
Pharmacokinetic: pembrolizumab[p]	See Table 5 for sample time points																		
Anti-NY-ESO-1 antibody		X[g]						X[g]						X[g]		X[g]		X[v]	X
Immune Response Biomarker (ELISpot)		X[g]			X	X		X[g]			X	X[h]		X[g,h]	X[h]	X[g,h]	X[h]	X[h,v]	X
Immune Response Biomarker (Tetramer)		X[g]				X		X[g]				X[h]		X[g,h]	X[h]	X[g,h]	X[h]	X[h,v]	X
Immune Cell Phenotyping		X[g]			X	X		X[g]			X	X[h]		X[g,h]	X[h]	X[g,h]	X[h]	X[h,w]	X
Cytokines		X[g]	X	X	X	X		X[g]	X	X	X	X[h]		X[g,h]	X[h]	X[g,h]	X[h]	X[h,w]	X
Circulating tumor DNA		X[g]						X[g]						X[g]		X[g]		X	X[x]
Archival Tumor Tissue[q]		X																	
Tumor Tissue, Fresh Biopsy		X[s]										X[t]							
Pulmonary function test	X[aa]													X[aa]				X[aa]	
Radiographic Disease Assessment[r]	X[r]	Every 56 ± 7 days																	
IRT Transaction	X	X						X						X		X		X	
ASP0739 Dosing		X						X						X		X			
Pembrolizumab Dosing[y]		X										X		Every 6 weeks after C2D15 dose				X	

Footnotes continued on next page

AE: adverse event; C: cycle; CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; ECHO: echocardiogram; 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; iRECIST: immune response evaluation criteria in solid tumors; IRT: interactive response technology; MRI: magnetic resonance imaging; MUGA: multiple gated acquisition scan; NY-ESO-1: New York esophageal squamous cell carcinoma 1; 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

a. Cycles 1 through 6 represent ASP0739 single agent or combination of ASP0739 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 ASP0739 as decided by the investigator.

c. After the first 4 cycles, participants who achieve PR or SD may continue further treatment of ASP0739 in cycles 5 and 6. Participants who reach CR will not receive additional doses of ASP0739.

d. Participants in combination therapy only will continue to receive pembrolizumab as monotherapy for doses 5 up to 17. If participant receives at least 1 dose of ASP0739 but discontinues combination treatment of ASP0739 at any time prior to C5D15, then the participant may continue pembrolizumab as monotherapy for up to 96 weeks for a total of 17 doses of pembrolizumab total for the study.

e. Height measurement performed at screening only. If height cannot be measured at the screening visit, it can be collected at any time during the course of the study, but should be recorded for the screening visit. Weight measurement performed at screening and day 1 of each cycle.

f. The following vital sign assessments schedules apply:

- At C1D1 and any visit when pembrolizumab and ASP0739 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 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 ASP0739 infusion, every 15 min (-5 to +10 min window) during ASP0739 infusion, at the end of ASP0739 infusion (-5 to +10 min window), and post dose (+30 min, +1, +2, +3 and +4 hours [± 10 min window each] from end of ASP0739 infusion).
- ASP0739 dosing only: vital signs will be obtained within 15 min prior to start of ASP0739 infusion, every 15 min (-5 to +10 min window) during ASP0739 infusion, at the end of ASP0739 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 ASP0739 infusion. If participants are still available, additional optional vital sign assessments 3 hours (± 10 min) and 4 hours (± 10 min) after completion of the ASP0739 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 pembrolizumab infusion; at the end of 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.

g. Obtain predose.

h. Obtain predose if participant receives pembrolizumab at the same visit.

i. If performed within 2 weeks of screening (prior to ICF and performed as part of standard of care), then do not need to be repeated. If participants present positive troponin levels or new onset of cardiovascular symptoms, MUGA or ECHO should be performed.

j. 12-lead ECGs will be recorded in triplicate (at least 2 min apart per time point) and read locally. On IP administration days, ECG will be obtained:

Footnotes continued on next page

- At C1D1 and any visit when pembrolizumab and ASP0739 are administered together: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of ASP0739.
- ASP0739 dosing only: ECGs are obtained predose (-1 h from start of ASP0739 infusion) and 1 to 2 h post dose of ASP0739.
- Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.

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

l. Urine or serum pregnancy test will be performed in women of childbearing potential. On treatment visit days, test must occur prior to IP administration.

m. 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. For participants in combination therapy arm, troponin levels will be obtained at screening; thereafter, weekly for 6 weeks and subsequently every second week for 6 weeks.

n. Thyroid panel including triiodothyronine or free triiodothyronine, free thyroxine and thyroid stimulating hormone will be measured prior to receiving pembrolizumab for participants in the combination cohort (Screening, C2D15 then every 6 weeks).

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

p. See Table 5 for collection schedule for ASP0739 single agent and ASP0739 and pembrolizumab combination therapy.

q. 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.

r. 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. Imaging will occur every 56 ± 7 days until confirmed progression by iRECIST.

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

t. Participants in all expansion cohorts are required to provide an on-treatment tumor specimen collected ± 7 days of the C2D15 visit (or unscheduled).

u. The EOT visit will occur within 7 days of the principal investigator decision to discontinue the participant for treatment or prior to the start of new anticancer treatment, whichever occurs first. If a participant is completing all visits in the last treatment cycle, the EOT visit will be within 7 days from the last planned visit.

v. Samples collected at pembrolizumab doses 5, 7, 9, 11 and 13 only.

w. Samples collected at pembrolizumab doses 5 and 7 only.

x. Sample collected at the time of discontinuation due to disease progression.

y. In the combination therapy arm, pembrolizumab will be administered as an intravenous infusion over 30 min followed by ASP0739 administration at least 1 hour after pembrolizumab administration. For participants enrolled in Japanese safety lead-in, C1D8 assessments should be performed prior to discharge from hospital.

z. If participant is completing all assessments within cycle 6, EOT assessment will be on C6D22 (± 3 days) or prior to the initiation of new anticancer therapy, whichever occurs first.

aa. Only participants in the combination therapy arm need to undergo pulmonary function tests at screening and at weeks 12 and 24 (before dose 3 and dose 5 of pembrolizumab, respectively) of study treatment.

bb. These assessments only apply to the Japanese participants.

Footnotes continued on next page

Table 3 Schedule of Assessments for Follow-up Periods

Visit	Safety Follow-up			Follow-up Period Year 1[a]	Survival Follow-up
	30 day[b]	60 day[b]	90 day[b]	Every 8 weeks[c]	Every 3 months
Window (days)	± 3	± 3	± 3	± 7	± 7
Physical Examination	X	X	X		
Vital Signs	X	X	X		
ECOG Performance	X	X	X		
Concomitant Medications	X	X	X		
12-Lead ECG	X	X	X		
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)	X	X	X		
Pregnancy Test for WOCBP	X	X	X		
AE/SAE Assessment	X	X	X		
Pharmacokinetic sample for cell kinetics (ASP0739)	See Table 5 for sample time points				
Blood Sample for NY-ESO-1 antibody	X	X	X	X[d]	
Blood Sample for Immune Response Biomarker (ELISpot)	X	X	X	X[e]	
Blood Sample for Immune Response Biomarker (Tetramer)	X	X	X	X[d]	
Blood Sample for Immune Cell Phenotyping	X	X	X	X[e]	
Blood Sample for Cytokines	X	X	X	X[e]	
Blood Sample for ctDNA	X	X	X	X[f]	
Radiographic Disease Assessment	Every 56 ± 7 days				
Survival Follow-up[g]					X

AE: adverse event; ctDNA: circulating tumor DNA; ECG: electrocardiogram; ECOG: eastern cooperative oncology group; ELISpot: enzyme-linked immunospot; EOT: end of treatment; NY-ESO-1: New York esophageal squamous cell carcinoma 1; SAE: serious adverse event; WOCBP: woman of childbearing potential

a. Follow-up visits every 2 months or until progression or start of a new anticancer therapy or death (whichever occurs first).

b. From the last dose.

Footnotes continued on next page

c. From EOT or the last planned assessment if EOT was not performed.
d. Maximum of 5 samples collected during Follow-up Period Year 1. Samples will be collected at the time of the disease assessment visit.
e. Maximum of 1 sample collected during Follow-up Period Year 1. Sample will be collected at the time of the disease assessment visit.
f. Sample will be collected at the time of discontinuation due to disease progression or the start of a new anticancer therapy.
g. Outcomes will be assessed by telephone calls every 3 months for up to 12 months.

Table 4 Schedule of Replication Competent Lentivirus for Dose Escalation Cohort, Dose Expansion Cohort and Safety Lead-in Cohort

Assessment	C1D1	3 Months after Treatment Initiation or End of Treatment, whichever is first	6 Months after Treatment Initiation	12 Months after Treatment Initiation	18 Months after Treatment Initiation
Window	0	± 7 day	± 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.

b. Obtained predose.

Table 5 Sample Collection Schedule- Dose Escalation Cohort, Dose Expansion Cohort and Safety Lead-in Cohort

Cycle	Day	Time Point	Window	Dose Escalation and Safety Lead-in[g]		Dose Expansion[h]	
				Pembrolizumab PK[a]	ASP0739 PK	Pembrolizumab PK[a]	ASP0739 PK
Cycle 1	1	Predose	- 60 min[b]	X	X	X	X
		End of Pembrolizumab Infusion	+ 10 min[c]	X		X	
		End of ASP0739 Infusion	+ 10 min[d]		X		X
		30-minute post ASP0739 Infusion	± 10 min		X		X
		1-hour post ASP0739 Infusion	± 10 min		X		X
		2-hour post ASP0739 Infusion	± 15 min		X		X
		5-hour post ASP0739 Infusion	± 15 min		X		X
	2	24-hour post ASP0739 Infusion	± 60 min		X		X[f]
	4	NA			X		
Cycle 2	1	Predose	- 60 min[e]		X		X
		End of ASP0739 Infusion	+ 10 min[d]		X		X[f]
		30-minute post ASP0739 Infusion	± 10 min		X		X[f]
		1-hour post ASP0739 Infusion	± 10 min		X		X[f]
		2-hour post ASP0739 Infusion	± 15 min		X		X[f]
		5-hour post ASP0739 Infusion	± 15 min		X		X[f]
	2	24-hour post ASP0739 Infusion	± 60 min		X		X[f]
	4	NA			X		
	15	Predose	- 60 min[b]	X			
		End of pembrolizumab Infusion	+ 10 min[c]	X			
Cycle 3	1	Predose	- 60 min[e]		X		
		End of ASP0739 Infusion	+ 10 min[d]		X		

Table continued on next page

Cycle	Day	Time Point	Window	Dose Escalation and Safety Lead-in[g]		Dose Expansion[h]	
				Pembrolizumab PK[a]	ASP0739 PK	Pembrolizumab PK[a]	ASP0739 PK
Cycle 4	1	Predose	- 60 min[b]	X	X	X[f]	X[f]
		End of pembrolizumab Infusion	+ 10 min[c]	X		X[f]	
		End of ASP0739 Infusion	+ 10 min[d]		X		X[f]
		30-minute post ASP0739 Infusion	± 10 min		X		
		1-hour post ASP0739 Infusion	± 10 min		X		
		2-hour post ASP0739 Infusion	± 15 min		X		
		5-hour post ASP0739 Infusion	± 15 min		X		
Cycle 5	1	Predose	- 60 min[e]		X		
		End of ASP0739 Infusion	+ 10 min[d]		X		
	15	Predose	- 60 min[b]	X			
		End of pembrolizumab Infusion	+ 10 min[c]	X			
Cycle 6	1	Predose	- 60 min[e]		X		
		End of ASP0739 Infusion	+ 10 min[d]		X		
EOT	EOT	NA		X	X	X	X
Safety Follow-up	30 days	NA			X		
Pembrolizumab Single Agent: Doses 5 and 6	1	Predose	- 60 min[b]	X	X	X	
		End of pembrolizumab Infusion	+ 10 min[c]	X		X	

C: cycle; D: day; EOT: end of treatment; NA: not applicable; PK: pharmacokinetics.

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

b. Within 60 min prior to pembrolizumab infusion (combination arm) or prior to ASP0739 infusion (single agent arm).

c. Within 10 min after the end of pembrolizumab infusion (before the infusion of ASP0739 on C1D1 and C4D1).

d. Within 10 min after the end of ASP0739 infusion.

e. Within 60 min prior to ASP0739 infusion.

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

g. For the participants who enroll in the Japanese safety lead-in for monotherapy, PK sampling will be taken at the times indicated for dose escalation and safety lead-in.

h. For Japanese participants who enroll after the Japanese safety lead-in is completed, PK sampling will be taken at the times indicated for dose expansion.

2 INTRODUCTION

In this study (0739-CL-0101), ASP0739 is indicated as a single agent and in combination with pembrolizumab in patients with advanced solid tumors known to express the tumor-associated antigen New York esophageal squamous cell carcinoma 1 (NY-ESO-1).

Details about ASP0739 are provided in the Investigator's Brochure.

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

2.1 Study Rationale

Cancer testis antigens (CTAs) have restricted expression in immune privileged organs (such as the testes and ovaries) and are silent in normal tissues. CTAs are stably expressed in many cancers and have high immunogenic potential [Gjerstorff et al, 2015]. In particular, NY-ESO-1 has high and frequent expression in malignant cancers [Jungbluth et al, 2001] and is able to elicit potent integrated natural humoral and cellular responses [Gnjatic et al, 2006]. ASP0739 has effects against NY-ESO-1 expressing tumors by inducing both natural killer cell activity (innate immunity) and NY-ESO-1-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 ASP0739 is active in NY-ESO-1 expressing tumors as described in Section 4.1.1.3 of the Investigator's Brochure. A synergistic effect of ASP0739 with anti-programmed cell death protein 1 (anti-PD-1) antibodies was observed in a nonclinical setting as detailed in Section 4.1.1.5 of the Investigator's Brochure. Therefore, ASP0739 as monotherapy or in combination with anti-PD-1 antibodies may result in clinical benefit for solid tumors known to express NY-ESO-1.

2.2 Background

ASP0739 is an aAVC product composed of human embryonic kidney 293 (HEK293) cells that can be transfected with a lentiviral vector to express the tumor-associated antigens, in this case NY-ESO-1, intracellularly and the antigen-presenting molecule, cluster of differentiation 1d, on the cell surface. These genetically engineered cells are then loaded with α Galactosylceramide (α-GalCer), followed by X-ray irradiation to inhibit ASP0739 cell proliferation. Another aAVC compound, ASP7517, which uses the same platform and only differs in the intracellularly expressed antigen (Wilms' Tumor 1 [WT1] instead of NY-ESO-1) is currently being evaluated in an ongoing clinical study (7517-CL-0101). ASP7517 and ASP0739 are similar in their ability to activate innate and adaptive immunity and have similar nonclinical toxicology profiles.

NY-ESO-1 has been identified as a robust biomarker predicting clinical benefits with anti-PD-1 monotherapy and is useful for decision making in clinical settings [Oka et al, 2020]. NY-ESO-1 is considered to be the most immunogenic CTA and is a target for cancer vaccine strategies that utilize the immune system [Esfandiary & Ghafouri-Fard, 2015]. It has been reported that about 75% of patients with cancer express NY-ESO-1 at some stage of their

illness [Barrow et al, 2006]. Several studies on the utility of NY-ESO-1 as a surrogate marker of clinical response in multiple myeloma [Leutkens et al, 2014], gastric cancer [Fujiwara et al, 2013] and other malignancies have been conducted. Antibodies against NY-ESO-1 were observed during disease progression in multiple myeloma [Leutkens et al, 2014], as well as in gastric cancer, with the frequency of antibody positivity increasing during disease progression for patients with gastric cancer [Fujiwara et al, 2013]. NY-ESO-1 protein expression has been detected in invasive melanomas [Giavina-Bianchi et al, 2015] with a positivity rate of 32% to 45% [Bolli et al, 2005; Vaughn et al, 2004], esophageal squamous cell carcinoma (ESCC) [Ueda et al, 2018] with a positivity rate of about 32% [Akcakanat et al, 2004] and non-small cell lung cancer (NSCLC) [Wang et al, 2019] with 12% to 25% of tumors testing positive [Bolli et al, 2005; Jungbluth et al, 2001]. Studies have confirmed the high frequencies of NY-ESO-1 expression in MRCL and synovial sarcoma (SS), [Endo et al, 2015; Lai et al, 2012; Jungbluth et al, 2001]. NY-ESO-1 expression has also been noted as a sensitive and specific diagnostic biomarker in myxoid/round cell liposarcoma (MRCL) [Hemminger et al, 2013; Pollack et al, 2012]. Early data have shown that NY-ESO-1 is a valid target to generate clinical response via immunological activation.

A detailed description of the chemistry, pharmacology, efficacy and safety of ASP0739 is provided in the Investigator's Brochure.

2.2.1 Synovial Sarcoma and Myxoid/Round Cell Liposarcoma

In the US, 13130 new patients (7470 males and 5660 females) are forecasted to be diagnosed with soft tissue sarcomas and 5350 patients are expected to die of the disease in 2020 [American Cancer Society, 2020]. For patients diagnosed with soft tissue sarcomas between 2009 and 2015, based on combined Surveillance, Epidemiology and End Results stages, the 5-year survival rate was 65% [American Cancer Society, 2020]. SS is an uncommon malignant tumor of the tissue around the joints with the most common locations being the extremities with distant pulmonary metastases developing in most patients after primary tumor surgery [Zhang et al, 2014]. SS accounts for about 5% to 10% of soft tissue tumors [Fisher, 1998]. About 50% of patients die within 10 years of diagnosis even with treatment [Terry et al, 2005]. MRCL is typically found in the lower extremities [National Institutes of Health, 2016]. Prognosis is better for patients with a low grade MRCL with a small percentage of round cells (5-year survival rate of 92%) whereas a greater percentage of round cells (5% or higher) is associated with a much poorer prognosis and a 5-year survival rate of 74% [Orphanet, 2013]. A systematic review of sarcoma survival rates indicated that 5-year survival rates for all patients with metastatic sarcoma were 20% to 25% for bone, and for soft tissue sarcoma 13% to 15% [Treasure et al, 2012]. About 88% of tumors in MRCL and 76% to 80% of tumors in SS express NY-ESO-1 [Endo et al, 2015; Lai et al, 2012; Jungbluth et al, 2001].

2.2.2 Ovarian Cancer

It is estimated that 21750 women will be newly diagnosed with ovarian cancer in the US in 2020 and 13940 will die of the disease in 2020 [American Cancer Society, 2020]. Ovarian cancer is predominantly diagnosed in postmenopausal women, and due to the lack of

symptoms in early stages, more than 75% of patients are diagnosed in advanced stages of the disease [Doubeni et al, 2016]. For patients with ovarian cancer, 5-year survival rates are below 45% [Webb & Jordan, 2017]. 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 (OS) is less than 15 months [Shimokawa et al, 2018]. About 43% of ovarian cancers express NY-ESO-1 [Odunsi et al, 2003].

2.3 Risk/Benefit Assessment

2.3.1 Risk Assessment

2.3.1.1 ASP0739 Risk Assessment

As of 06 May 2022, 4 participants have received ASP0739; therefore, the safety profile, RP2D and possible contraindications of ASP0739 have not been established. However, preliminary data from 4 participants who have received at least 1 dose of ASP0739 1×10^7 cells/dose in the dose escalation phase of Study 0739-CL-0101 have not identified any DLTs or safety concerns.

ASP7517, another aAVC compound, uses the same platform as ASP0739 and only differs in the intracellularly expressed antigen (WT1 instead of NY-ESO-1). ASP7517 currently has 2 ongoing clinical studies (7517-CL-0101 and 7517-CL-1101). As of 05 Oct 2021, 19 participants have received at least 1 dose of ASP7517 at dose levels of 1×10^6 cells/dose, 1×10^7 cells/dose and 1×10^8 cells/dose. The RP2D for ASP7517 in participants with R/R acute myeloid leukemia and R/R higher risk myelodysplastic syndromes was determined to be 1×10^8 cells/dose. No DLTs in doses of up to 1×10^8 cells/dose have been identified.

While different target antigens allow targeting different tumor types, no differences in the clinical safety profiles are expected between ASP0739 and ASP7517; this is supported by the very similar nonclinical safety profiles of both compounds. Target organs of toxicity for ASP7517 in nonclinical studies were primarily the liver, spleen and kidney, with minor non-toxicologically significant findings noted in pancreas, urinary bladder and epididymides.

Table 6 Summary of Potential Safety Concerns for ASP0739

Target Organs/ Systems	Potential Risks from Nonclinical Studies	Risk Minimization and/or Characterization Action
Liver	Increased liver weight, elevated AST and ALT levels, emboli, hepatocyte focal necrosis, mixed inflammatory cell infiltration, microgranuloma, granulomatous inflammation, mononuclear cell aggregation, and pigment laden macrophage infiltration	Close monitoring of liver function via laboratory assessments of liver function
Hematology	Decreased followed by increased platelet counts. Increased RBC parameters, decreased WBC and lymphocyte counts	Standard laboratory assessment of hematology
Table continued on next page		

Target Organs/ Systems	Potential Risks from Nonclinical Studies	Risk Minimization and/or Characterization Action
Kidney	Increased serum creatinine. Basophilic tubules and infiltration of mononuclear cells	Standard monitoring of kidney function parameters (creatinine, blood urea nitrogen) and urinalysis
Spleen	Increased weight, apoptosis in lymphoid follicles, emboli, lymphoid follicular hyperplasia	Standard laboratory assessment of hematology
General	Immune-Mediated Adverse Reaction, Cytokine-release syndrome – Not observed non-clinically	Close monitoring of participant's signs or symptoms; Chemokine/Cytokine panel and tryptase level.
	Infusion-Related Reaction – Not observed non-clinically	Close monitoring of participant's signs or symptoms; Chemokine/Cytokine panel and tryptase level.
	Immunotoxicity directed against non-target toxicity (testis and placenta) - Risk cannot be ruled out based on nonclinical studies. However, as NY-ESO-1 is only expressed in immune privileged organs, the risk is considered low [Raza et al, 2020].	Close monitoring of participant's signs or symptoms; Testosterone testing in male participants
	Allergic Reactions and Anaphylaxis – Not observed non-clinically	Close monitoring of participant's signs or symptoms; Chemokine/Cytokine panel and tryptase level.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; RBC: red blood cells; WBC: white blood cell

- **Liver Toxicity:** Close monitoring of liver function and toxicities is required during clinical studies. The liver is a target organ of toxicity for ASP0739, which is related to the activation of the innate immune system by α-GalCer. The hepatic findings in mice included increased liver weight, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, emboli, hepatocyte focal necrosis, mixed inflammatory cell infiltration, microgranuloma, granulomatous inflammation, mononuclear cell aggregation and pigment laden macrophage infiltration. The hepatic findings of increased AST and ALT 1 day after administration of ASP0739 were completely reversed following a 28-day recovery period.
- **Hematology:** The standard assessment of hematology is recommended in clinical studies. A dose-related decrease in platelet count was seen 1 day after the first and 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.
- **Kidney:** The standard monitoring of kidney function parameters (creatinine, blood urea nitrogen) is recommended in clinical studies. Increased serum creatinine was noted 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 first and 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.
- **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 follicles of the spleen 1 day after the first or second dose. This

finding was completely resolved by 7 days following ASP0739 administration. Also, extramedullary hematopoiesis and lymphoid follicular hyperplasia occurred 7 days after the first and second dose and resolved by 28 days. Standard hematology testing is recommended in clinical trials.

- **Infusion-related Reactions:** In nonclinical studies with ASP0739, infusion-related reactions (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 (SOC).
- **Allergic Reactions and Anaphylaxis:** Based on the nonclinical data, no signs or symptoms of allergic reaction or anaphylaxis were seen following ASP0739 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 SOC.

Other

Adverse events (AEs) reported from solid tumor early phase clinical studies 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 adverse events (SAEs) were treatment related [Ishikawa et al, 2005; Kunii et al, 2009; Motohashi et al, 2009; Uchida et al, 2008].

The AEs reported in early phase NY-ESO-1-peptide vaccine clinical studies in patients with advanced solid tumors were mainly grade 1 or 2 events including injection site pain, fatigue, nausea, vomiting, pain, diarrhea and hyperkalemia [Mahipal et al, 2019; Odunsi et al, 2007].

In addition, based on the above and the mechanism of action of ASP0739, immune-related AEs (irAEs) such as fever, headache, fatigue, hot flashes, diarrhea, muscular and joint pain should be considered and managed as required per SOC.

2.3.1.2 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 ASP0739 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 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 the study.

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

- Enrollment within each dose escalation cohort will be staggered such that there will be a minimum of 28 calendar days between the treatment initiation of the first and second participants and 14 calendar days between the second and the third participants. In the absence of toxicity, additional participants may be treated at a dose level without any formal stagger. An interval of 28 calendar days will separate study treatment initiation of the last participant in a dose cohort from the first patient enrollment in sequential dose cohort.
- 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 [Liu & Yuan, 2015] 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.

- A Tolerability Evaluation Meeting (TEM) consisting of sponsor representatives and investigators will convene once the number of Japanese participants [Section 10.1.5.1 Tolerability Evaluation Meeting] completes the DLT observation period and data are available for review.
- The safety in the expansion cohorts will be monitored using Bayesian logistic model based on all DLT data obtained up to that time from both escalation cohorts and expansion cohorts and drug-related 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 Statistical Considerations].

The potential risk of irAEs and 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 ASP0739 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 SOC and published guidelines, as appropriate based on investigator judgment, and on the protocol instructions regarding interruption or discontinuation of treatment.

2.3.3 Benefit Assessment

No clinical studies have been completed; therefore, the antitumor activity of ASP0739 in humans is unknown. The nonclinical data suggest ASP0739 may have activity against NY-ESO-1 expressing tumors; therefore, participants with SS and MRCL as well as ovarian cancer and other NY-ESO-1 expressing tumors may receive clinical benefit from participation in this study. Based on the preclinical data, the clinical benefit of ASP0739 may be enhanced by combination with pembrolizumab.

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 by the FDA to treat metastatic melanoma, NSCLC, SCLC, head and neck squamous cell cancer, classical Hodgkin lymphoma, primary mediastinal B-cell lymphoma, urothelial cancer, gastric cancer, esophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, endometrial carcinoma, tumor mutational burden-high cancer, cutaneous squamous cell carcinoma and any unresectable or metastatic solid tumor with microsatellite instability and DNA mismatch repair deficiency. Pembrolizumab may improve the effect of ASP0739 since the inhibition of

the binding of PD-1 to its ligands prevents immune evasion by cancer cells. As such, aAVC would prime the immune system and make cancer cells more susceptible to effector T-cells that have been activated by ASP0739.

Preclinical models suggest that ASP0739 treatment combinations with PD-1 pathway blockade may provide additive antitumor effect over treatment with either one alone.

The majority of patients treated with the current SOC including with anti-PD-1 monotherapies, when indicated, 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

ASP0739 has effects against NY-ESO-1 expressing tumors and showed no significant safety findings in the preclinical pharmacology studies. In the mice repeated dose toxicity studies of ASP0739, all major findings were reversible and monitorable and will not interfere with human clinical studies considering its potential benefit against the risk. The clinical safety profile at identical doses of ASP7517 was acceptable and this is expected to be similar for ASP0739.

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 ASP0739 and a PD-1 inhibitor, no overlapping toxicity is expected given that NY-ESO-1 is limited to the tumor.

Overall, the risk associated with participation in this clinical study of ASP0739 as a 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 have a contraindication to all therapy with established clinical benefit for their malignancy.

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 AND ENDPOINTS

Table 7 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
● To evaluate the safety and tolerability of ASP0739 in participants with R/R solid tumors known to express NY-ESO-1 when administered as a single agent (phase 1 dose escalation), and in combination with pembrolizumab in participants with R/R SS, MRCL and ovarian cancer (safety lead-in)	● Safety and tolerability as noted by: DLTs, AEs, SAEs, laboratory test results (serum chemistry, hematology, coagulation, urinalysis and pregnancy test), ECGs, vital signs, physical exams and ECOG performance status scores
● To determine RP2D of ASP0739 when administered as a single agent	● RP2D based on above
● To evaluate the clinical response of ASP0739 when administered as a single agent and in combination with pembrolizumab in participants with R/R SS, MRCL and ovarian cancer (phase 2)	● Objective response rate per iRECIST (iORR) by Independent Central Review
Secondary	
● To evaluate other measures of anticancer activity of ASP0739 when administered as a single agent and in combination with pembrolizumab based on central and local assessment in participants with R/R SS, MRCL or ovarian cancer (phase 2)	● 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)
● To obtain preliminary efficacy based on central and local assessment in participants with R/R solid tumors known to express NY-ESO-1 (melanoma, NSCLC-adenocarcinoma and squamous cell and ESCC) (phase 2)	● Objective response rate per iRECIST (iORR)

Table continued on next page

Objectives	Endpoints
Exploratory	
• To evaluate potential genomic, proteomic and/or other biomarkers that may correlate with treatment outcome when ASP0739 is administered as a single agent and in combination with pembrolizumab	• Exploratory biomarkers that may correlate with treatment outcome of ASP0739 as a single agent or in combination with pembrolizumab, including NY-ESO-1 expression
• To evaluate pharmacodynamic activities of ASP0739 as a single agent and in combination with pembrolizumab	• Pharmacodynamic effects of ASP0739, such as changes in: o Cytokine expression and secretion (e.g., IFNg) o NY-ESO-1-specific T lymphocytes (e.g., cytotoxic T lymphocytes) o Immune cell populations (NKT cells, Treg cells, etc.) o Anti-NY-ESO-1 antibodies o Tumor microenvironment (CD8, PD-L1, etc.)
• To evaluate pharmacokinetics of ASP0739 when administered as a single agent and in combination with pembrolizumab	• Cellular DNA load and kinetic parameter estimates (including AUC, C_{max}, C_{trough} and t_{max}) for ASP0739 as a single agent or in combination with pembrolizumab

AE: adverse event; CD8: cluster of differentiation 8; DCR: disease control per RECIST v1.1; DLT: dose limiting toxicity; DOR: duration of response per RECIST v1.1; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ESCC: esophageal squamous cell carcinoma; iDCR: disease control per iRECIST; iDOR: duration of response per iRECIST; IFNg; interferon gamma; iORR: objective response rate per iRECIST; iPFS: progression-free survival per iRECIST; iRECIST: immune response evaluation criteria in solid tumors; MRCL: myxoid/round cell liposarcoma; NKT: natural killer T; NSCLC: non-small cell lung cancer; NY-ESO-1: New York Esophageal-1; ORR: objective response rate per RECIST v1.1; OS: overall survival; PD-L1: programmed death-ligand 1; PFS: progression-free survival per RECIST v1.1; R/R: relapsed/refractory; RECIST: response evaluation criteria in solid tumors; RP2D: recommended phase 2 dose; SAE: serious adverse event; SS: synovial sarcoma

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Overall Study Design

This is a phase 1, open-label study of ASP0739 in participants with R/R solid tumors known to express NY-ESO-1 and a phase 2 study of single agent and combination therapy with pembrolizumab in participants with R/R SS, MRCL or ovarian cancer.

Phase 1 (dose escalation) in participants with solid tumors known to express NY-ESO-1 and phase 2 of ASP0739 single agent and combination therapy with pembrolizumab in R/R SS, MRCL and ovarian cancer who have not responded to SOC or are ineligible for standard therapy. Phase 2 single agent will also include a cohort of participants with select solid

tumors known to express NY-ESO-1 (melanoma, NSCLC-adenocarcinoma and squamous cell and ESCC).

Both study phases consist of the following periods:

- Screening (up to 28 days)
- Treatment with ASP0739 (up to 6 doses every 28 days) and for participants in combination cohorts with pembrolizumab on cycle 1 day 1 (C1D1), and then every 6 weeks, until disease progression, unacceptable toxicity or up to 17 doses
- EOT visit after completion of IP: Within 7 days of EOT determination or prior to the initiation of new anticancer therapy, whichever occurs first
- Safety follow-up visits at 30, 60 and 90 days from the last dose of treatment or prior to the initiation of new anticancer therapy
- Follow-up visits every 2 months for up to 1 year or until progression or start of a new anticancer therapy or death (whichever occurs first)
- Survival follow-up for up to 1 year by telephone calls every 3 months after the start of a new anticancer treatment or progression after ASP0739 and/or pembrolizumab treatment

ASP0739 Single Agent

Participants will receive an intravenous infusion of ASP0739 (HEK293 transfected with a lentiviral vector that is encoding the target antigen NY-ESO-1). Participants will receive 1 dose every 28-day cycle for up to 4 doses; an additional 2 doses may be administered in participants with a partial response (PR) or stable disease (SD). Following the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit may continue further treatment with ASP0739, as decided by the investigator.

ASP0739 Combination with Pembrolizumab

The recommended phase 2 dose (RP2D) of ASP0739 determined from the phase 1 dose escalation phase will be combined with pembrolizumab 400 mg for the safety lead-in with approximately 6 to 9 participants. If the RP2D is selected at the same dose level as the maximum tolerated dose (MTD) based on the phase 1 dose escalation portion, the combination safety lead-in will start at one dose level lower than the MTD.

If DLTs occur in the safety lead-in cohort and the dose level is de-escalated to a lower dose level per BOIN design (either from 1×10^8 to 1×10^7 or from 1×10^7 to 1×10^6), the dose de-escalation cohort enrollment must be completed and determined to be safe by the DESC before enrollment in the ASP0739 and pembrolizumab combination expansion cohorts.

Participants will receive 1 dose of ASP0739 every 28-day cycle for a total of 4 doses; an additional 2 doses may be administered for participants with PR or SD. Following the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit may continue further treatment with ASP0739 and pembrolizumab, as decided by the investigator. Participants will also receive pembrolizumab 400 mg on C1D1, then every 6 weeks, until disease progression, unacceptable toxicity or for up to 17 doses or until one of the discontinuation criteria is met. For combination treatment, a

400 mg pembrolizumab infusion will be administered first, followed by an ASP0739 infusion at least 1 hour after the completion of the pembrolizumab infusion.

Phase 1 Single Agent Dose Escalation:

The single agent dose escalation phase will evaluate escalating dose levels of ASP0739 in approximately 3 to 12 DLT-evaluable participants.

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

Table 8 Dose Levels (Phase 1 Dose Escalation)

Dose Level	Dose
0	1×10^7 cells/dose
+1	1×10^8 cells/dose

The dose escalation phase will assess safety and tolerability of ASP0739 during cycle 1. Participants will receive up to 6 doses of ASP0739 via intravenous infusion separated by 28 days. Dosing will occur on day 1 of each cycle. After the first dose of ASP0739, participants must be observed for safety for a minimum of 4 hours. If new AEs are observed that are greater than grade 3 during this time, participants should continue to be observed until the AEs are less than grade 3.

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 phase will enroll 3 to 4 evaluable participants for the initial assessment of each dose level. Refer to the *Participant Replacement during Dose Escalation/Safety Lead-in* section for definition of evaluable participants. Enrollment within each dose escalation cohort will be staggered such that there will be a minimum of 28 calendar days between the treatment initiation of the first and second participants and 14 calendar days between the second and third participants at the same dose level for all escalation cohorts. In the absence of toxicity, additional participants may be treated at a dose level without any formal stagger. An interval of 28 calendar days will separate study treatment initiation of the last participant in a dose cohort from the first patient enrollment in sequential dose cohort. If the decision is made to remain at the current dose level, an additional 3 or 4 evaluable participants may be enrolled in the current dose level. A minimum of 6 participants must be enrolled at the dose level used to determine the RP2D.

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

Action	Number of Participants Treated at Current Dose Level					
	3	**4**	**5**	**6**	**7**	**8**
Escalate dose if number of participants with DLT ≤	0	0	1	1	1	1
Stay at current dose level if number of participants with DLT =	1	1	NA	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; NA; not applicable

Definition of DLTs for ASP0739 Single Agent:

A DLT is defined as any of the following events that occur within 28 days starting with the first dose on C1D1 in the dose escalation cohort and that is considered to be possibly, probably or definitely related to IP. Confirmation of DLTs will be made by the DESC. The severity of AEs will be assessed according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE), v5.0. Participants experiencing DLTs, who in the opinion of the investigator are deriving clinical benefit from the study treatment (e.g., marked reduction in tumor burden), may be allowed to continue study treatment with ASP0739 upon resolution of the event to ≤ grade 1 or baseline, upon discussion with the sponsor. Participants experiencing DLTs during the single agent dose escalation phase will not be replaced.

DLTs are defined as follows:

- Grade ≥ 2 autoimmune reaction
- Grade 3 irAEs that do not resolve to grade ≤ 1 in 3 to 5 days
- Grade 4 irAEs
- Grade ≥ 3 non-hematological AE that does not resolve to grade ≤ 2 within 72 hours of onset
- Grade 4 neutropenia
- Grade 3 febrile neutropenia with or without infection
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia accompanied by bleeding that requires any transfusion
- Grade 4 anemia
- Grade 3 anemia requiring transfusion
- AST or ALT > 5 × upper limit of normal (ULN; grade ≥ 3) without liver metastases
- AST or ALT > 8 × ULN in participants with liver metastases
- AST or ALT > 3 × ULN and total bilirubin (TBL) > 2 × ULN (in participants with Gilbert syndrome: AST or ALT > 3 × ULN and direct bilirubin > 1.5) (confirmed Hy's Law)
- Grade ≥ 3 liver function test abnormality lasting ≥ 7 days

- Grade 5 toxicity
- Prolonged delay (> 2 weeks) in initiating cycle 2 due to treatment-related toxicity

The following AEs will not be considered DLTs:

- 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 of onset
- 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 within 72 hours of onset with standard antiemetic or antidiarrheal medications used at prescribed dose
- 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 ASP0739 will be considered to be a DLT
- Grade 3 or lower irAEs that resolve to ≤ grade 1 within 72 hours of onset after starting treatment including corticosteroids

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 be discontinued from treatment.
- 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 be discontinued from treatment.
- If there is a delay in administration of the second cycle by > 4 weeks, it would result in discontinuation from treatment after discussion with the sponsor.

ASP0739 in Combination with Pembrolizumab Safety Lead-in

Enrollment in the combination therapy safety lead-in will start once phase 1 single agent dose escalation is completed and the RP2D is defined.

The combination therapy safety lead-in portion will evaluate the RP2D of ASP0739 with a fixed dose of 400 mg pembrolizumab in 6 to 9 participants with at least 6 DLT-evaluable participants. If the RP2D is selected at the same dose level as the MTD based on the phase 1 dose escalation portion, the combination safety lead-in will start at one dose level lower than the MTD.

Safety lead-in will be guided according to the BOIN design [Liu & Yuan, 2015] to determine if the RP2D of ASP0739 with a fixed dose of 400 mg pembrolizumab is tolerable and based on DLT occurrence after 28 days. After the planned number of evaluable participants has completed the DLT observation period of 28 days for a given dose level, safety for that dose level will be assessed. Safety lead-in will enroll 3 to 4 evaluable participants for the initial assessment of RP2D. A minimum of 6 participants must be enrolled at the dose level used to determine the RP2D. Enrollment will be staggered such that there will be a minimum of 28 calendar days between the treatment initiation of the first and second participants, as well as 14 calendar days between the second and third participants at the same dose level for the safety lead-in cohort. In the absence of toxicity, additional participants may be treated at a dose level without any formal stagger. An interval of 28 calendar days will separate study treatment initiation of the last patient in a dose cohort from the first participant treatment in sequential dose cohort.

Action	Number of Participants Treated at Current Dose Level					
	3	**4**	**5**	**6**	**7**	**8**
Escalate dose if number of participants with DLT ≤	0	0	1	1	1	1
Stay at current dose level if number of participants with DLT =	1	1	NA	2	2	2
De-escalate if number of participants with DLT = [a]	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; NA; not applicable

a. Dose de-escalation will be implemented as a single dose level reduction to a lower dose of ASP0739 (either from 1×10^8 to 1×10^7 or from 1×10^7 to 1×10^6) in combination with pembrolizumab 400 mg.

Definition of DLTs for ASP0739 and Pembrolizumab Combination Therapy

A DLT is defined as any of the following events that occur within 28 days starting with the first dose on C1D1 in the safety lead-in cohort and that is considered to be possibly, probably or definitely related to ASP0739 and/or pembrolizumab. Confirmation of DLTs will be made by the DESC. The severity of AEs will be assessed according to NCI-CTCAE, v5.0. Participants experiencing DLTs, who in the opinion of the investigator are deriving clinical benefit from the study treatment (e.g., marked reduction in tumor burden), may be allowed to continue study treatment with ASP0739 upon resolution of the event to ≤ grade 1 or baseline, upon discussion with the sponsor. Participants experiencing DLTs during the combination safety lead-in portion will not be replaced.

DLTs are defined as follows:

- Grade ≥ 2 autoimmune reaction
- Grade 3 irAEs that do not resolve to grade ≤ 1 in 3 to 5 days
- Grade 4 irAE
- Grade ≥ 3 non-hematological AE that does not resolve to grade ≤ 2 within 72 hours of onset
- Grade 4 neutropenia

- Grade 3 febrile neutropenia with or without infection
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia accompanied by bleeding that requires transfusion or hospitalization
- Grade 4 anemia
- Grade 3 anemia requiring transfusion
- AST or ALT > 5 × ULN (grade ≥ 3) without liver metastases
- AST or ALT > 8 × ULN in participants with liver metastases
- AST or ALT > 3 × ULN and TBL > 2 × ULN (in participant with Gilbert syndrome: AST or ALT > 3 × ULN and direct bilirubin > 1.5) (confirmed Hy's law)
- TBL > 3 × ULN (grade ≥ 3)
- Grade ≥ 3 liver function test abnormality lasting ≥ 7 days
- Grade 5 toxicity
- Prolonged delay (> 2 weeks) in initiating cycle 2 due to treatment-related toxicity
- Grade ≥ 2 pneumonitis
- Grade ≥ 2 encephalopathy, meningitis, or motor or sensory neuropathy
- Guillain-Barré syndrome or myasthenic syndrome/myasthenia gravis
- Infusion-related reaction that requires the infusion to be discontinued

The following AEs will not be considered DLTs:

- 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 of onset
- 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 within 72 hours of onset with standard antiemetic or antidiarrheal medications used at prescribed dose
- Grade 3 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 ASP0739 and/or pembrolizumab will be considered to be a DLT
- Grade 3 or lower irAEs that resolve to ≤ grade 1 within 72 hours of onset after starting treatment including corticosteroids

Participants who are tolerating ASP0739 and/or pembrolizumab at a dose level that is being reviewed due to the occurrence of DLTs in another participant will not be automatically precluded from continued dosing during the safety review, and will be allowed to continue dosing for as long as tolerated unless directed otherwise as a result of the safety review by the DESC.

Dose escalation within individual participants will not be allowed. Refer to the *Participant Replacement during Dose Escalation/Safety Lead-in* section for definition of evaluable participants.

DLTs Requiring Discontinuation of Treatment

- If a study participant develops a grade 4 DLT after receiving cycle 1, then the study participant should be discontinued from treatment.
- 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 be discontinued from treatment.
- If there is a delay in administration of the second cycle by > 4 weeks, it would result in discontinuation from treatment after discussion with the sponsor.

Study Enrollment Interruption:

Study enrollment will be temporarily interrupted pending review of the following:

- Any death that is not related to disease progression occurring within 30 days of receiving ASP0739 and/or pembrolizumab
- Occurrence of 2 grade ≥ 4 DLTs in 2 study participants
- Any grade 4 hypersensitivity reaction/anaphylaxis

Participant Replacement during Dose Escalation/Safety Lead-in:

Participants may be replaced in the safety lead-in or dose escalation cohort if:

- Participant is discovered to have enrolled without fully satisfying eligibility criteria.
- Participant did not receive the planned dose in cycle 1 for reasons other than DLT.
- Participant has no DLT and withdraws from the study before the end of the DLT evaluation period.

The decision to replace participants will be made by the sponsor based on the above criteria.

Recommended Phase 2 Dose

The sponsor, in conjunction with the DESC, will determine the RP2D of ASP0739 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 ASP0739.

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

Dose Escalation 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 for the phase 1 dose escalation and safety lead-in. 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 expansion and phase 2 expansion cohorts for single agent and combination therapy with pembrolizumab.

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 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 RP2D dose for expansion will not be higher than the MTD. If the RP2D is selected at the same dose level as the MTD based on the phase 1 dose escalation portion, the combination safety lead-in will start at one dose level lower than the MTD.

Phase 2 Single Agent

Once RP2D is determined, the phase 2 single agent cohorts may be opened in R/R SS, MRCL, ovarian cancer and other solid tumors known to express NY-ESO-1 (melanoma, NSCLC-adenocarcinoma and squamous cell and ESCC). If a confirmed response (partial response based on iRECIST [iPR] or complete response based on iRECIST [iCR], per independent central review or local assessment) occurs in other solid tumors known to express NY-ESO-1, a tumor-specific dose expansion cohort may be opened in that tumor type.

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]. For R/R SS, MRCL and ovarian cancer, initially 18 participants will be enrolled in each tumor-specific expansion cohort (stage 1). If the iORR does not meet the optimal stopping boundaries (see table below), then an additional 25 participants (stage 2) may be enrolled for a total maximum sample size of 43 participants. When the total number of participants reaches the maximum sample size of 43, it may be predicted that ASP0739 is effective if the number of responses is greater than or equal to 8.

Optimized Stopping Boundaries for SS, MRCL and Ovarian Cancer	
Number of participants treated	**Stop if number of responses ≤**
18	2

MRCL: myxoid/round cell liposarcoma; SS: synovial sarcoma

For the melanoma/NSCLC/ESCC cohort, after a minimum of 10 participants per tumor type are enrolled, if less than approximately 6 participants for each tumor type of melanoma, NSCLC-adenocarcinoma or squamous cell carcinoma or ESCC are NY-ESO-1 positive upon analysis of the most recent tissue sample, then additional participants may be enrolled into the tumor type with less than approximately 6 NY-ESO-1 positive participants.

UNIQUE to Japan Sites:

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

Phase 2 Single Agent Dose Expansion Cohort with Japanese Safety Lead-in

After the phase 1 dose escalation cohort has been completed, the phase 2 single agent dose expansion cohort with Japanese safety lead-in will be opened. The Japanese safety lead-in will enroll 3 to 8 safety evaluable participants to confirm Japanese tolerability of the RP2D of ASP0739. Japanese participants must be managed under hospitalization for 7 days from C1D1 through C1D8 during the Japanese safety lead-in. Prior to hospital discharge, the investigator must ensure participant safety by performing medical tests and procedures listed on Day 8 of Cycle 1. During the Japanese safety lead-in, an interval of 7 days will separate study treatment initiation for the second participant from the first participant. In the absence of toxicity, additional participants may be treated without any formal stagger.

The tolerability of ASP0739 single agent therapy RP2D will be assessed during the DLT observation period, which is from C1D1 to C1D28. Quantitative assessment of DLTs will be performed referring to the concept of a BOIN design with the target DLT rate of 30% and optimal interval of (0.236, 0.359) to determine if the ASP0739 single agent therapy RP2D is tolerable and is based on a DLT occurrence after 28 days. The tolerability evaluation rule is as follows:

	Number of Participants evaluable for DLT Assessment					
	3	**4**	**5**	**6**	**7**	**8**
[Tolerable] If the number of participants with DLTs is equal or less than the number given in the corresponding cell, the ASP0739 single agent therapy RP2D can be determined to be tolerable.	0	0	1	1	1	1
[Stay] If the number of participants with DLTs is equal to the number given in the corresponding cell, enrollment is continued until the maximum number of participants is reached.	1	1	NA	2*	2*	2*
[Not tolerable] If the number of participants with DLTs is equal or greater than the number given in the corresponding cell, the ASP0739 single agent therapy RP2D is determined to be intolerable.	2	2	2	3	3	3

DLT: dose limiting toxicity; NA: not applicable; RP2D: recommended phase 2 dose; TEM: tolerability evaluation meeting

*When the number of participants for DLT assessment reaches the maximum number of participants and the recommended action is Stay, the tolerability of the dose will be assessed comprehensively at the TEM.

A minimum of 3 evaluable participants must be enrolled at the dose level used to determine the tolerability of RP2D in Japanese participants. Three to four safety evaluable participants are enrolled as initial assessment. If the evaluation is to be continued based on DLT

occurrence, additional 3 to 4 safety evaluable participants are enrolled. After the tolerability of RP2D is confirmed in Japanese participants, additional Japanese participants will be enrolled into dose expansion part continuously.

Tolerability Evaluation Meeting

A TEM consisting of sponsor representatives and investigators will convene once the number of Japanese participants [Section 10.1.5.1 Tolerability Evaluation Meeting] completes the DLT observation period and data are available for review. TEM members should consider all available safety findings when making their evaluations and decisions. Additional details regarding responsibilities, membership requirements and safety review time points are included in the TEM Charter.

Replacement of Participants in Japanese Safety Lead-in

Participants may be replaced in the safety lead-in if:

- The participant is discovered to have enrolled without fully satisfying the eligibility criteria.
- The participant received less than the planned dose in C1 for reasons other than a DLT.
- The participant has experienced 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 safety lead-in will not be replaced.

The 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 ASP0739 upon resolution of the DLT event to ≤ grade 1 or baseline.

A participant who meets the stopping criteria will not be receive study drug at C2. Additionally, at the TEM, the aggregate safety data are reviewed if any study stopping rules below have been met:

- If a study participant develops a grade 4 DLT after receiving C1
- If a study participant develops a grade ≥ 3 non-hematological AE that does not resolve to ≤ grade 2 within 72 hours of onset
- Note: This event should be considered a DLT.
- If there is a delay in administration of C2 by > 4 weeks, it may result in discontinuation of treatment after discussion with the sponsor.

Study enrollment and study treatment of the Japanese safety lead-in will be temporarily interrupted if any of the following events occur in a participant:

- Any death that is not related to disease progression occurring within 30 days of receiving ASP0739

- Occurrence of 2 grade ≥ 4 DLTs in 2 participants
- Any grade 4 hypersensitivity reaction/anaphylaxis

Phase 2 Combination of ASP0739 + Pembrolizumab

Once safety lead-in is completed and 2 radiographic responses (iCR or iPR) are observed in the phase 2 dose expansion monotherapy cohort by local or central review, the phase 2 combination cohorts may be opened in the respective tumor type where the responses were observed.

For R/R SS, initially 22 participants will be enrolled in an expansion cohort (stage 1). If the iORR does not meet the optimal stopping boundaries (see table below) for R/R SS, then an additional 38 participants (stage 2) may be enrolled for a total maximum sample size of 60. When the total number of participants reaches the maximum sample size of 60, it may be predicted that ASP0739 in combination with pembrolizumab is effective if the number of responses is greater than or equal to 18.

Optimized Stopping Boundaries for SS	
Number of participants treated	**Stop if number of responses ≤**
22	3

SS: synovial sarcoma

For R/R MRCL, initially, 22 participants will be enrolled in an expansion cohort (stage 1). If the iORR does not meet the optimal stopping boundaries (see table below) for R/R MRCL, then an additional 38 participants (stage 2) may be enrolled for a total maximum sample size of 60. When the total number of participants reaches the maximum sample size of 60, it may be predicted that ASP0739 in combination with pembrolizumab is effective if the number of responses is greater than or equal to 18.

Optimized Stopping Boundaries for MRCL	
Number of participants treated	**Stop if number of responses ≤**
22	3

MRCL: myxoid/round cell liposarcoma

For R/R ovarian cancer, initially, 10 participants will be enrolled in an expansion cohort (stage 1). If the iORR does not meet the optimal stopping boundaries (see table below) for R/R ovarian cancer, then an additional 19 participants (stage 2) may be enrolled for a total maximum sample size of 29. When the total number of participants reaches the maximum sample size of 29, it may be predicted that ASP0739 in combination with pembrolizumab is effective if the number of responses is greater than or equal to 4.

Optimized Stopping Boundaries for Ovarian Cancer	
Number of participants treated	**Stop if number of responses ≤**
10	0

If both single agent and combination therapy expansion cohorts are open for the same tumor type, participants will be randomized to either single agent or combination therapy cohorts

and the randomization ratio will be based on the number of open slots still available at each cohort.

Replacement of Participants in Phase 2 Dose Expansion

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

4.2 Scientific Rationale for Study Design

This study was designed to evaluate ASP0739 as monotherapy and in combination with pembrolizumab in selected participants with advanced solid tumors known to express the NY-ESO-1 antigen. Antitumor efficacy of ASP0739 was demonstrated in preclinical studies. In a murine metastatic cancer model, a suppression of lung metastases in mice was observed, and in a murine melanoma model, a suppression of tumor growth.

The rationale for evaluating the combination of ASP0739 and pembrolizumab is supported by preclinical data obtained from a murine melanoma model that shows superior antitumor activity of combination therapy over monotherapy. ASP0739 is an aAVC expressing NY-ESO-1. Tumor volume was suppressed in animals receiving aAVC-NY-ESO-1 treatment in combination with anti-PD1 antibody relative to aAVC-NY-ESO-1 or anti-PD1 antibody alone. This suggests additive activity of ASP0739 with checkpoint inhibitors like pembrolizumab, which are known to restore immune system tumor surveillance, while ASP0739 functions by priming and activating the immune system against NY-ESO-1 tumor cells. 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 confirm safety for this combination.

In this study, each participant will receive ASP0739 as single agent or in combination with pembrolizumab every 28 days. To ensure participant safety, each escalation cohort will stagger treatment initiation to 28 calendar days between the treatment initiation of the first and second participants and 14 calendar days between the second and third participants at the same dose level for all escalation cohorts (as a single agent) or the safety lead-in cohort (for combination with pembrolizumab). In the absence of toxicity, additional participants may be treated at a dose level without any formal stagger.

The design will closely monitor safety while efficiently assessing efficacy of ASP0739 dose levels of 1×10^7 cells/dose and 1×10^8 cells/dose as monotherapy and in combination at the single agent RP2D with pembrolizumab fixed dose of 400 mg every 6 weeks, until disease progression, unacceptable toxicity or up to 17 doses. To ensure that a starting dose of ASP0739 in combination with pembrolizumab is safe, the combination cohort will only start once the RP2D of ASP0739 single agent dose escalation is completed and determined to be safe by the DESC. The combination therapy will start with a safety lead-in cohort with RP2D determined from single agent dose escalation. If the RP2D is selected at the same dose level

as the MTD based on the phase 1 dose escalation portion, the combination safety lead-in will start at one dose level lower than the MTD.

Tumor-specific expansion cohorts for ASP0739 monotherapy will begin following the determination of RP2D. The types of cancer for the expansion cohorts were selected based on expression of NY-ESO-1 in the tumor. Combination therapy in respective cancer cohort groups may begin once 2 local or central radiographic responses have been observed.

Participants with human immunodeficiency virus will be excluded since a compromised immune system may affect the immune response induced by ASP0739.

Objective response rate (ORR) is selected as a suitable primary efficacy endpoint in such an early phase study because it can be generally assessed early and with a smaller sample size compared with survival studies. In addition, ORR 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 ASP0739 as monotherapy and in combination with pembrolizumab in the selected participants.

4.3 Dose Rationale

4.3.1 ASP0739

The starting dose of ASP0739 is set at 1×10^7 cells/dose by intravenous infusion. This dose for the FIH study is anticipated to be safe with some pharmacological activity, as supported by the nonclinical studies and the ongoing FIH study for ASP7517 (7517-CL-0101) in which no DLTs were observed during the dose escalation phase, which includes 3 dose levels: 1×10^6 cells/dose, 1×10^7 cells/dose and 1×10^8 cells/dose (highest dose determined to be tolerable by DESC; currently enrolling additional patients for confirmation of safety). The only difference between ASP0739 and ASP7517 is the antigen, NY-ESO-1 instead of WT1. Different antigens allow for targeting different tumor types without expected changes to the safety profile.

Nonclinical pharmacology data suggest that the minimum biologically-active dose of ASP0739-surrogate or ASP0739 is 5×10^3 cells/mouse, since natural killer T (NKT) cell activation with anti-tumor effect was observed at this dose level or higher. The dose of 5×10^3 cells/mouse is calculated as 1.7×10^5 cells/kg (5×10^3 cells/30 g) and estimated to be 1×10^7 cells/dose/human (1.7×10^5 cells/kg $\times$ 60 kg). The starting dose for the FIH study was also assessed based on the results of the nonclinical toxicology studies. Toxicities (e.g., liver findings, changes in platelet count) were observed after ASP0739 intravenous administration at the lowest dose used in nonclinical studies (1×10^5 cells/kg: equivalent to 6×10^6 cells/dose, administered per 60 kg human), and the no-observed-adverse-effect level was not established in those studies. However, the observed toxicity profile is similar to that of ASP7517 and it was noted that the toxicities are reversible and monitorable in the nonclinical studies. While ASP7517 expresses WT1, ASP0739 expresses NY-ESO-1;

however, the primary mode of toxicity is considered to be related to α-GalCer, which is part of the construct in both ASP7517 and ASP0739 in similar amounts. The difference in antigen targeting is not expected to increase toxicity, and may be decreased for ASP0739, because WT1 is reported to be expressed in several tissues including testis, kidney and mesothelium [Maki et al, 2017], whereas NY-ESO-1 is reported to be selectively expressed in the testis only [Raza et al, 2020; Jungbluth et al, 2001].

From these nonclinical results and the observed safety data in Study 7517-CL-0101 using the same aAVC platform, the recommended starting dose for the FIH study for ASP0739 is 1×10^7 cells/dose. The dose level will be escalated to 1×10^8 cells/dose (highest dose in study 0739-CL-0101), since nonclinical data showed reversible and monitorable toxicities across the proposed investigational doses.

The dosing regimen for the FIH study consists of repeated dosing in 28-day intervals. Since nonclinical pharmacology data suggest immune cells are further stimulated by repeated doses of aAVC with 4-week interval, an additive pharmacology effect could occur with this extended treatment regimen. Repeated doses (2 doses 28 days apart) resulted in a similar safety profile in mouse toxicity studies, including severity and frequency of findings, when compared with single dose administration. Also, there were no safety findings specific to the second dosing period, i.e., no cumulative toxicities were observed. Therefore, the currently available data support repeat dosing in the clinical setting. Following the first 2 cycles, participants who have not met any individual treatment discontinuation criteria and are receiving clinical benefit, may continue further treatment with ASP0739 (up to a total of 6 doses) and pembrolizumab, as decided by the investigator.

4.3.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 400 mg every 6 weeks, until disease progression, unacceptable toxicity or for a total of 17 doses or until one of the discontinuation criteria is met. For combination treatment, a 400 mg pembrolizumab infusion will be administered first, followed by an ASP0739 infusion at least 1 hour after the completion of the pembrolizumab infusion.

Recently, the manufacturer of pembrolizumab (Merck) has gained regulatory approval for a more convenient dosage in adult patients 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 patients whose weights are higher than average, with occupancy of 97% for patients 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., Health Insurance Portability and Accountability Act authorization for US study sites) must be obtained from the participant or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Participant is at least 18 years of age and legally an adult according to local regulation at the time of signing the ICF.
3. Phase 1 Dose Escalation only:
   - Participant has R/R solid tumor known to express NY-ESO-1 (examples are, but not limited to, gastric cancer, melanoma, ESCC, NSCLC, MRCL, SS, hepatic, SCCHN or ovarian cancer) after completing available SOC therapy or is not a candidate for SOC therapy. NY-ESO-1 expression status is not required for participant entry.
4. Safety lead-in, Phase 2 Single agent and Combination Therapy only:
   - Participant has R/R SS or MRCL disease after undergoing available SOC treatment or is not a candidate for SOC therapy (must have previously received either an anthracycline or ifosfamide containing regimen or another systemic regimen, if not a candidate for either agent).
     - Participant has not received prior checkpoint inhibitor therapy (i.e., PD-1/PD-L1 treatment naïve)
     - SS: confirmation by the presence of a translocation between SYT on the X chromosome and SSX1, SSX2 or, SSX4 on chromosome 18 (may be presented in the pathology report as t [X; 18]). If unconfirmed, enrollment into the study should be discussed with the medical monitor.

    - MRCL: confirmation by the presence of the reciprocal chromosomal translocation t (12;16) (q13;p11) or t(12; 22) (q13;q12). If unconfirmed, enrollment into the study should be discussed with the medical monitor.
- Participant has R/R ovarian cancer that is:
    - platinum resistant
      OR
      platinum-sensitive, but the participant is not a candidate for platinum or other SOC therapy.
    - Participant has not received prior checkpoint inhibitor therapy (i.e., naïve PD-1/PD-L1 treatment patients).
- Participant has R/R solid tumor (melanoma, NSCLC-adenocarcinoma and squamous cell or ESCC) after available SOC treatment or is not a candidate for SOC therapy (single-agent only).

5. Participant consents to provide an archival tumor specimen in a tissue block or unstained serial slides prior to IP administration. If an archival tissue sample is not available, enrollment into the study should be discussed with the medical monitor.
6. Participant in phase 2 consents to provide tumor specimen obtained within 56 days prior to first dose of study treatment, as tissue block or unstained serial slides. 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.
7. Participant in phase 2 consents to undergoing a tumor biopsy (core needle biopsy or excision) during the treatment period as indicated in the schedule of assessments.
8. Participant has an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
9. Participant with life expectancy of ≥ 12 weeks at the time of screening.
10. Participant must meet the following criteria as indicated on the clinical laboratory tests during screening period:
    - Serum AST and ALT $\leq 2.5 \times$ ULN (or $< 5 \times$ ULN if known liver metastases)
    - Serum TBL $\leq 1.5 \times$ ULN (or $< 3 \times$ ULN if known liver metastases)
    - Serum creatinine $\leq 1.5 \times$ ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation.
    - Platelets $\geq 100000/\mu L$
    - ANC $\geq 1500/\mu L$
    - Hemoglobin ≥ 9 g/dL
    - Prothrombin time/international normalized ratio (PT/INR) $< 1.5 \times$ ULN unless on warfarin.
    - PTT $< 1.5 \times$ institutional normal limits.
11. A female participant is eligible to participate if she is not pregnant [Section 10.2 Appendix 2: Contraception Requirements] and at least one of the following conditions apply:
    - Not a woman of childbearing potential (WOCBP) as defined in [Section 10.2 Appendix 2: Contraception Requirements]
      OR

- WOCBP who agrees to follow the contraceptive guidance as defined in [Section 10.2 Appendix 2: Contraception Requirements] throughout the treatment period and for at least 6 months after the final IP administration.

12. Female participant must not be breastfeeding at screening or during the study period and for 6 months after the final IP administration.
13. Female participant must not donate ova at screening and throughout the study period and for 6 months after the final IP administration.
14. A male participant with female partner(s) of childbearing potential must agree to use contraception as detailed in [Section 10.2 Appendix 2 Contraception Requirements] during the treatment period and for at least 6 months after the final IP administration.
15. Male participant must not donate sperm starting at screening and throughout the study period and for 6 months after the final IP administration.
16. Participant agrees not to participate in another interventional study while on treatment.
17. Participant has measurable disease according to RECIST 1.1. For participant with only 1 measurable lesion and prior radiotherapy, the lesion must be outside the field of prior radiotherapy or must have documented progression following radiation therapy.

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 has persistent non-hematological toxicities of ≥ grade 2 (NCI-CTCAE v5.0), with symptoms and objective findings from treatment (including chemotherapy, kinase inhibitors, immunotherapy, experimental agents, radiation or surgery).
2. Participant has received any of the following therapies (for inclusion in the study, all abnormalities must have returned to ≤ grade 1):
   - Systemic immunomodulators (checkpoint inhibitors) - except the dose escalation phase and the NY-ESO-1 solid tumor (melanoma, NSCLC-adenocarcinoma and squamous cell and ESCC) cohorts in the dose expansion phase of monotherapy, which may have received prior checkpoint inhibitor therapy
   - Immunosuppressive drugs including steroids ≤ 14 days prior to treatment
   - Cytotoxic agents ≤ 14 days prior to treatment
   - Investigational agent ≤ 21 days prior to treatment or 5 half-lives, whichever is shorter
   - Radiation therapy ≤ 21 days prior to treatment
3. Participant has clinically active or untreated nervous system metastases. Participants with previously treated central nervous system (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 study treatment 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.

4. Participant has an active autoimmune disease. Participant 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.
5. 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.
6. Participant has known history of serious hypersensitivity reaction to a known ingredient of ASP0739 or pembrolizumab or severe hypersensitivity reaction to treatment with another monoclonal antibody.
7. Participant has a prior malignancy active (i.e., requiring treatment or intervention) within the previous 2 years prior to 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.
8. Participant has received a prior allogeneic bone marrow or solid organ transplant.
9. Participant has an active uncontrolled infection within 14 days of treatment.
10. Participant is known to have human immunodeficiency virus infection.
11. Participant has active hepatitis B or C or other active hepatic disorder or participant is on hepatitis treatment. Hepatitis C RNA testing is not required in participants with negative hepatitis C antibody testing.
12. Participant has any condition which, in the investigator's opinion, makes the participant unsuitable for study participation.
13. Participant has had a major surgical procedure and has not completely recovered within 28 days prior to the start of study treatment.
14. Participant has had a myocardial infarction or unstable angina within 6 months prior to the start of study treatment 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.
15. Participant is expected to require another form of anti-cancer therapy while on study treatment.
16. This criterion has been removed.
17. Participant has a known or suspected hypersensitivity to bovine-derived protein or has suspected hypersensitivity to any ingredients of ASP0739.

Additional Exclusion Criteria for Participants in Combination Therapy Cohorts

1. Participants with a history of myocarditis or congestive heart failure (as defined by New York Heart Association Functional Classification III or IV), as well as unstable angina, serious uncontrolled cardiac arrhythmia, uncontrolled infection, or myocardial infarction 6 months prior to study entry.
2. Participants with active interstitial lung disease (ILD)/pneumonitis or a history of ILD/pneumonitis requiring treatment with systemic steroids.
3. Participants with baseline pulse oximetry < 92% "on Room air."

4. Participants must not have known microsatellite instability-high or deficient MisMatch Repair.

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 be resolved 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 must be entered into screening with a new participant identification number. Rescreening is only allowed once for an individual participant.

6 INVESTIGATIONAL PRODUCT(S)

6.1 Investigational Product(s) Administered

Table 9 Investigational Product(s)

Name	**ASP0739**	**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	The solution is clear to slightly opalescent, colorless to slightly yellow
Unit Dose Strength	[redacted] CCI [redacted]	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 or obtained locally

IMP: Investigational Medicinal Product

Refer to the pharmacy manual for detailed information regarding preparation, handling and storage of ASP0739.

Refer to the approved pembrolizumab package insert, summary of product characteristics, monograph or local product information supplied by the manufacturer for additional instructions for drug preparation and dilution.

6.1.1 Investigational Product Administration

ASP0739 will be diluted with Lactated Ringer's injection to approximately 50 mL and administered by intravenous infusion at 4 to 6 mL/min infusion rate through a dedicated intravenous line every 28 days during treatment beginning on C1D1.

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 the ASP0739 injection for participants in the ASP0739 and pembrolizumab combination therapy arms.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

Sponsor-provided IP used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at Astellas Pharma Global Development, Inc. (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 safety lead-in portion of the ASP0739 and pembrolizumab combination arm when both phase 2 single agent dose expansion and combination therapy safety lead-in are open.

If both single agent and combination therapy expansion cohorts are open for the same tumor type, participants will be randomized to either single agent or combination therapy cohorts and the randomization ratio will be based on the number of open slots still available at each cohort.

UNIQUE to Japan Sites:

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

6.4 Investigational Product 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 ASP0739 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 AE after receiving a dose of ASP0739 may receive the subsequently scheduled dose of ASP0739 only after the observed grade 3 AE has resolved to grade 1; the subsequent dose of ASP0739 may be reduced by one dose level, either from 1×10^8 to 1×10^7 cells/dose or from 1×10^7 to 1×10^6 cells/dose.

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 [Sections 10.8 Appendix 8: Infusion Reaction Dose Modification and Treatment (Guidelines for ASP0739 and Pembrolizumab); 10.10 Appendix 10: Dose Modification and Toxicity Management for Immune-related Adverse Events; and 10.11 Appendix 11: Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab] and the 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

ASP0739 will be given up to a maximum of 6 cycles. ASP0739 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 ASP0739 does not have authorization to be administered after the study is complete.

6.7 Treatment of Overdose

In the event of suspected ASP0739 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 ≥ 2.5 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.

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:

- The use of systemic steroids (> 30 mg per day of hydrocortisone or > 10 mg per day of prednisone or equivalent) is not allowed during study treatment unless needed to manage AEs related to study treatment. 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 study treatment (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is also allowed. Corticosteroids to manage irAEs are permitted.
- Immunosuppressive agents including but not limited to, high dose steroids, mammalian target of rapamycin inhibitors (e.g., rapamycin) or mycophenolate mofetil.
- Investigational agents other than ASP0739 and pembrolizumab.
- Any other cancer directed therapies are prohibited during the study with ASP0739 and ASP0739 and pembrolizumab, including chemotherapy, biologic therapy, radiation therapy or surgery.
    - *Palliative (limited field) radiation therapy:* for bone metastases is allowed. Study treatment 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.
- Vaccines: Live vaccines are prohibited while the participant is receiving study treatment and for 30 days after last dose of study treatment. 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-Guérin and typhoid vaccine.
    - COVID-19 prevention is allowed if non-live vaccines are to be used. In cases where a live vaccine is needed for COVID-19 prevention, please contact the medical monitor for discussion.

Refer to [Section 10.5 Appendix 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 3]. 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 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 SOC 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 complete response (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 progressive disease (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 3] 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.
- Laboratory assessments must be submitted for centralized data entry.

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 3].
- 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 of rest and will include temperature, systolic and diastolic blood pressure and pulse.

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 3]. 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. If height cannot be measured at the screening visit, it can be collected at any time during the course of the study but should be recorded for the screening visit.

7.2.4 Electrocardiogram

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

- At C1D1 and any visit when pembrolizumab and ASP0739 are administered together, ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of ASP0739.
- ASP0739 dosing only: ECGs are obtained predose (-1 h from start of ASP0739 infusion) and 1 to 2 h post dose of ASP0739.
- Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.

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

Radiographic disease assessment is to be performed at screening and throughout the study every 56 ± 7 days. The 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 SOC are acceptable as screening scans, if done within 28 days prior to C1D1.

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 3].

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 and other procedures, or that caused the participant to discontinue the IP and other 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 3] 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 3] 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 of an SAE/AE 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 pre-dose 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 10.3.7 Reporting Procedures for Special Situations]) 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 an 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 an 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]. 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 IRRs are 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 ASP0739 cells via determination of genomic DNA in the cell by a quantitative polymerase chain reaction method for the dose escalation cohort, expansion cohort and safety lead-in cohort. Sampling time points are as shown in the schedule of assessments [Table 5].

Serum concentrations of pembrolizumab will be evaluated in the combination therapy arm, including safety lead-in, as outlined in the schedule of assessments [Table 5].

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

7.5 Pharmacodynamics/Biomarker

Samples for exploratory pharmacodynamics and biomarker analyses of ASP0739 will be collected according to the schedules of assessments [Table 1 and Table 2].

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 ASP0739.

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-NY-ESO-1 antibodies, cytokine expression and secretion (e.g., IFNg), NY-ESO-1-specific T lymphocytes (e.g., cytotoxic T lymphocytes), immune cell populations (e.g., NKT cells, NK cells, etc.), expression levels of NY-ESO-1 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 NY-ESO-1, 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 (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 4]. 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 of 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 will be from participants on C1D1 and will not exceed 80 mL; the maximum amount of blood collected in one cycle will be during C1 and will not exceed 130 mL.

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 that, in the opinion of the investigator, indicates continued treatment is not in the best interest of the participant.

- In the combination therapy arm only, treatment will be permanently discontinued following occurrence of grade 3 to 4 myocarditis.
- 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/or the participant is no longer deriving clinical benefit, in the opinion of the investigator.
- Participant begins other anti-cancer therapies.
- Participant experiences disease relapse/progression.
- Investigator/subinvestigator determines that the continuation of the study treatment will be detrimental to the participant.
- Participant is in need of receiving prohibited concomitant treatment(s) based on Investigator's clinical opinion.
- 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 schedule of assessments [Table 3]. 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 schedule of assessments [Table 3].

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

Phase 2 Single Agent (SS, MRCL, Ovarian)

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.

Solid tumors known to express NY-ESO-1 (melanoma, NSCLC-adenocarcinoma and squamous cell as well as ESSC)

There is no formal statistical hypothesis for this cohort.

Phase 2 Combination Therapy

SS

H0: iORR is 20%, at which the treatment is deemed as unacceptable.
H1: iORR is at least 35%, at which the treatment is deemed as acceptable.

MRCL

H0: iORR is 20%, at which the treatment is deemed as unacceptable.
H1: iORR is at least 35%, at which the treatment is deemed as acceptable.

Ovarian

H0: iORR is 5%, at which the treatment is deemed as unacceptable.
H1: iORR is at least 20%, at which the treatment is deemed as acceptable.

9.2 Sample Size Determination

ASP0739 Single Agent

A total of approximately 181 participants may be enrolled in single agent treatment.

Phase 1 Single Agent Dose Escalation:

The sample size of approximately 12 participants for the dose escalation phase 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, a minimum of 6 evaluable and up to 12, should provide adequate information for the dose escalation and safety objectives of the study.

Phase 2 Single Agent:

It is estimated that up to approximately 169 participants may be enrolled in the single agent arms. The iORR is monitored using the BOP2 design.

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

The sample size of approximately 40 participants for other solid tumors known to express NY-ESO-1 is not based on statistical power calculation. A minimum of 10 participants per tumor type will be enrolled. If less than approximately 6 participants within each tumor type of melanoma, NSLCC-adenocarcinoma or squamous cell and ESCC are NY-ESO-1 positive based on analysis of the most recent tissue sample, additional participants may be added so that there are approximately 6 NY-ESO-1 positive participants.

ASP0739 Combination with Pembrolizumab:

A total of approximately 158 participants may be enrolled in combination therapy.

Combination Therapy Safety Lead-in

The sample size of approximately 6 to 9 participants for safety lead-in 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 safety objectives of the study.

Phase 2 Combination Therapy:

It is estimated that up to approximately 149 participants may be enrolled in the combination therapy arms. The iORR is monitored using the BOP2 design.

For each indication, with assumptions mentioned in the statistical hypotheses section, the statistical power would be approximately at least 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 1 dose of study treatment.
Response Analysis Set (RAS)	The response analysis set will consist of all participants who are enrolled and receive at least 1 dose of IP and have at least 1 post baseline primary efficacy measurement.
Safety Analysis Set (SAF)	All participants who take at least 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 the 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 the 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 nonmissing observation prior to the first administration of IP, unless otherwise specified.

In general, dose escalation and safety lead-in data will be summarized by dose level. Phase 2 data will be summarized by monotherapy and combination therapy arms and by tumor types, unless specified otherwise.

Demographics and baseline characteristics will be summarized 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, for participants in the safety analysis set (SAF). Similar tables for screening disposition, follow-up period disposition and survival follow-up disposition will also be presented for all treated participants. 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. IP exposure will be summarized using descriptive statistics and will be listed.

9.4.2 Analysis of Efficacy

Binary efficacy endpoint analysis will be conducted on the response analysis set (RAS), while time to event endpoints will be conducted on the full analysis set (FAS). The interpretation of results of the primary efficacy endpoint will be based on the RAS. 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

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 used for 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 used for 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 by 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.

9.4.3.1 Adverse Events

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

A treatment-emergent adverse event (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 single agent and combination therapy arms, by dose level, and overall and by time point. Shifts from baseline to the worst grade based on NCI-CTCAE v5.0 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 single agent and combination therapy arms, 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 single agent and combination therapy arms, by dose level and by time point.

Interpretations of routine 12-lead ECG results will be summarized by single agent and combination therapy arms, by dose level and by 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 ASP0739 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 ASP0739 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

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 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 a 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 during which 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 International Ethical Guidelines
  - Applicable ICH 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 or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative 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 or their legally authorized representative.

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. A copy of the signed 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 Tolerability Evaluation Meeting

UNIQUE to Japan Sites:

A TEM consisting of sponsor representatives and investigators will convene once the number of Japanese participants (defined in the protocol) completes the DLT observation period and data are available for review. TEM members should consider all available safety findings when making their evaluations and decisions. Additional details regarding responsibilities, membership requirements and safety review time points are included in the TEM Charter.

10.1.5.2 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.

While safety data from the DLT observation period in the escalation cohorts and the safety lead-in 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 MTD selected by BOIN design, based on evaluation of the safety data and other available data.

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., CROs).
- 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 in the CRF.
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, archived, 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 CRF 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 CRO(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, CRFs and source documents. Direct access to these documents will be required by the auditors.

- QTLs will be predefined in the applicable plan(s) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

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 months 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], 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 an 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 NCI-CTCAE guidelines, v5.0. The items that are not stipulated in the NCI-CTCAE, v5.0 will be assessed according to the criteria below and entered into the eCRF:

Table 11 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.

Specific to Japan Sites:

In the case of an 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 OYOBIFUGUAI 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 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:

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

Astellas Pharma Inc. – Japan
Pharmacovigilance
Fax number +3-3243-5747
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 6 months 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 Events] 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 an 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.

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 IPs, 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 quality assurance 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

An urgent safety measure (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 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 12 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 an 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 are prohibited, with the exception of immune-related AEs.

10.5.2 Other Investigational Agents

Treatment with investigational agents other than ASP0739 or pembrolizumab 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 13 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, Fibrinogen)	Activated partial thromboplastin time (aPTT) International normalized ratio (INR) Prothrombin time (sec) (PT) Fibrinogen
Thyroid Panel (combination cohort only)	Triiodothyronine or free triiodothyronine Free thyroxine Thyroid stimulating hormone

eCRF: electronic case report form; hCG: human chorionic gonadotrophin; PT/INR: prothrombin time/international normalized ratio.

†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 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 ASP0739 and Pembrolizumab)

Table 14 Infusion Reaction Dose Modification and Treatment (Guidelines for ASP0739 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 hours.	• **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 hr of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr. to 50 mL/hr.). 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 treatment (pembrolizumab only)**	**Pembrolizumab only:** Participant may be premedicated 1.5 hours (± 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 ASP0739 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 hours 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.		

hr: hour; NCI: National Cancer Institute; NSAID: non-steroidal anti-inflammatory drug; po: by mouth

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

Table 15 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 Adverse Events

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 16.

Based on the mechanism of action of ASP0739, 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]) and managed as required per SOC. 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 16 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

General instructions: 1. Severe and life-threatening 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		
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	

Table continued on next page

irAEs	Toxicity grade (CTCAE v5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
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
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		

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: common terminology criteria for adverse events; GI: gastrointestinal; irAE: immune-related adverse event; IV: intravenous; T1DM: Type 1 diabetes mellitus; ULN: upper limit of normal

Footnotes continued on next page

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

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

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 17.

Table 17 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 hours.	• **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 hr of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr. to 50 mL/hr.). 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 hours (± 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		

hr: hour; 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 4] unless the site principal investigator 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 Study Design and Dose Rationale] 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 principal investigator 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 patients 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 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 poses an additional risk to the participant's health and safety

Adherence to the original protocol as reflected in the schedule of assessment Table 1 to Table 4 is expected, where plausible, in the case of a crisis. The alternate measures as noted in Table 18 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 IP and maintaining critical safety and efficacy assessments for patients 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 Schedule of Assessments in Response to a Crisis

No alternative measures are permissible for C1D1 and ASP0739 and/or pembrolizumab dosing days during combination therapy.

Table 18 Study Interruption: Schedule of Assessments – Dose Escalation Cohort and Safety Lead-in Combination Cohort

	Alternate Approach(es)	Treatment[a]																				Pembro-lizumab Mono-therapy	EOT[e,w]
		Cycle 1						Cycle 2						Cycles 3 to 4[b]				Cycles 5 to 6[c]				Doses 5 to 17[d]	
Visit Days		**1**	**2**	**4**	**8**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22[w]**	**Every 6 weeks**	
Window (days)			0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	+ 7
Physical Examination[f]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI	X[f]	X		X	X	X	X[f]	X		X	X	X	X[f]	X	X	X	X[f]	X	X	X	X[f]	X[f]
Vital Signs[g]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained remotely via telemedicine visit or at local facility and results submitted to PI	X[h]	X		X	X	X	X[h]	X		X	X[h]	X	X[h]	X	X	X	X[h]	X	X	X	X[h]	X

Table continued on next page

	Alternate Approach(es)	Treatment[a]																				Pembro-lizumab Mono-therapy	EOT[e,w]
		Cycle 1						Cycle 2						Cycles 3 to 4[b]				Cycles 5 to 6[c]				Doses 5 to 17[d]	
Visit Days		**1**	**2**	**4**	**8**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22[w]**	**Every 6 weeks**	
Window (days)			0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	+ 7
12-Lead ECG[i]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI. If cannot be performed, Astellas medical monitor to assess for study continuation.	X[i]			X	X		X[i]			X	X[i]		X[i]				X[i]					X
Prior and Concomitant Medications	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained remotely via telemedicine visit	X	X		X	X	X	X	X		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 clinic and result submitted to PI	X[j]						X[j]						X[j]				X[j]				X[j]	X[j]
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[k]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI	X[h]	X		X	X	X	X[h]	X		X	X	X	X[h]	X	X	X	X[h]	X	X	X	X[h]	X

Table continued on next page

	Alternate Approach(es)	Treatment[a]																				Pembro-lizumab Mono-therapy	EOT[e,w]
		Cycle 1						Cycle 2						Cycles 3 to 4[b]				Cycles 5 to 6[c]				Doses 5 to 17[d]	
Visit Days		**1**	**2**	**4**	**8**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22[w]**	**Every 6 weeks**	
Window (days)			0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	+ 7
Coagulation Profile (PT/INR, fibrinogen)[k]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI	X[h]	X		X	X	X	X[h]	X		X	X	X	X[h]				X[h]				X[h]	X
Thyroid Profile Panel[k,l]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI											X		Every 6 weeks after C2D15 dose									
PGx[m]	None	X[m]																					
Buccal Swab for HLA Typing	None	X[h]																					
AE/SAE Assessment	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained remotely via telemedicine visit	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic: ASP0739[n]	None	See Table 5 for detailed sample time points																					

Table continued on next page

	Alternate Approach(es)	Treatment[a]																				Pembro-lizumab Mono-therapy	EOT[e,w]
		Cycle 1						Cycle 2						Cycles 3 to 4[b]				Cycles 5 to 6[c]				Doses 5 to 17[d]	
Visit Days		**1**	**2**	**4**	**8**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22[w]**	**Every 6 weeks**	
Window (days)			0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	+ 7
Pharmacokinetic: Pembrolizumab[n]	None	See Table 5 for detailed sample time points																					
Anti-NY-ESO-1 antibody	None	X[h]						X[h]						X[h]				X[h]				X[t]	X
Immune Response Biomarker (ELISpot)	None	X[h]			X	X		X[h]			X	X		X[h]	X	X		X[h]	X	X		X[t]	X
Immune Response Biomarker (Tetramer)	None	X[h]				X		X[h]				X		X[h]		X		X[h]		X		X[t]	X
Immune Cell Phenotyping	None	X[h]			X	X		X[h]			X	X		X[h]	X	X		X[h]	X	X		X[u]	X
Cytokines	None	X[h]	X	X	X	X		X[h]	X	X	X	X		X[h]	X	X		X[h]	X	X		X[u]	X
Circulating Tumor DNA	None	X[h]						X[h]						X[h]				X[h]				X	X[v]
Archival Tumor Tissue[o]	None	X																					
Pulmonary function test[x]	May be obtained at local facility and results submitted to PI													X								X	

Table continued on next page

	Alternate Approach(es)	Treatment[a]																				Pembro-lizumab Mono-therapy	EOT[e,w]
		Cycle 1						Cycle 2						Cycles 3 to 4[b]				Cycles 5 to 6[c]				Doses 5 to 17[d]	
Visit Days		**1**	**2**	**4**	**8**	**15**	**22**	**1**	**2**	**4**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22[w]**	**Every 6 weeks**	
Window (days)			0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	± 1	± 1	± 1	± 3	+ 7
Radiographic Disease Assessment[p]	May be collected locally and submitted to PI. Assessment to be done per protocol requirements. Outside of the window, assessments need to be escalated to Astellas medical monitor	Every 56 ± 7 days																					
ASP0739 Dosing[r]	None	X						X						X				X				X	
Pembrolizumab Dosing[s]	Every other dose may be administered locally during Pembrolizumab monotherapy only, otherwise must be administered at study site.	X										X		Every 6 weeks[s]								X	

AE: adverse event; C: cycle; CR: complete response; CT: computed tomography; D: day; ECG: electrocardiogram; ECHO: echocardiogram; 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; MUGA: multiple gated acquisition scan; NY-ESO-1: New York esophageal squamous cell carcinoma 1; 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

a. Cycles 1 through 6 represent ASP0739 single agent or combination of ASP0739 and pembrolizumab therapy; each ASP0739 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 ASP0739 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 ASP0739 in cycles 5 and 6. Participants who reach CR will not receive additional doses of ASP0739.

Footnotes continued on next page

d. Participants in combination therapy only will continue to receive pembrolizumab as monotherapy for doses 5 up to 17. If participant receives at least 1 dose of ASP0739 but discontinues combination treatment of ASP0739 at any time prior to C5D15, then the participant may continue pembrolizumab as monotherapy for up to 96 weeks for a total of 17 doses of pembrolizumab total for the study.

e. The EOT visit will occur within 7 days of the PI decision to discontinue the participant for treatment or prior to the start of new anticancer treatment, whichever occurs first. If a participant is completing all visits in the last treatment cycle, the EOT visit will be within 7 days from the last planned visit.

f. Height measurement performed at screening only. If height cannot be measured at the screening visit, it can be collected at any time during the course of the study, but should be recorded for the screening visit. Weight measurement performed at screening and day 1 of each cycle.

g. The following vital sign assessments schedules apply:

- At C1D1 and any visit when pembrolizumab and ASP0739 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 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 ASP0739 infusion, every 15 min (-5 to +10 min window) during ASP0739 infusion, at the end of ASP0739 infusion (-5 to +10 min window), and post dose (+30 min, +1, +2, +3 and +4 hours [± 10 min window each] from end of ASP0739 infusion).
- ASP0739 dosing only: vital signs will be obtained within 15 min prior to start of ASP0739 infusion, every 15 min (-5 to +10 min window) during ASP0739 infusion, at the end of ASP0739 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 ASP0739 infusion. If participants are still available, additional optional vital sign assessments 3 hours (± 10 min) and 4 hours (± 10 min) after completion of the ASP0739 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 pembrolizumab infusion; at the end of 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.

h. Obtain predose.

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

- At C1D1 and any visit when pembrolizumab and ASP0739 are administered together, ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of ASP0739.
- ASP0739 dosing only: ECGs are obtained predose (-1 h from start of ASP0739 infusion) and 1 to 2 h post dose of ASP0739.
- Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.

j. Urine or serum pregnancy test will be performed in women of childbearing potential. 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. For participants in combination therapy arm, troponin levels will be obtained at screening; thereafter, weekly for 6 weeks and subsequently every second week for 6 weeks.

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 (Screening, C2D15 then every 6 weeks).

Footnotes continued on next page

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

n. See Table 5 for collection schedule for ASP0739 single agent and ASP0739 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. Imaging will occur every 56 ± 7 days until confirmed progression by iRECIST.

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

r. In both the monotherapy and combination cohorts, each participant must remain at the site facility for 4 hours following the participant's first dose of ASP0739. For the next dose (second dose) or additional subsequent single agent with ASP0739, participants must remain at the site facility for at least 2 hours after ASP0739 dosing.

s. In the combination therapy arm, pembrolizumab will be administered as an intravenous infusion over 30 min followed by ASP0739 administration at least 1 hour after pembrolizumab administration. For participants enrolled in Japanese safety lead-in, C1D8 assessments should be performed prior to discharge from hospital.

t. Samples collected at pembrolizumab doses 5, 7, 9, 11 and 13 only.

u. Samples collected at pembrolizumab doses 5 and 7 only.

v. Sample collected at the time of discontinuation due to disease progression.

w. If participant is completing all assessments within cycle 6, EOT assessment will be on C6D22 (± 3 days) or prior to the initiation of new anticancer therapy, whichever occurs first.

x. Only participants in the combination therapy arm need to undergo pulmonary function tests at screening and at Weeks 12 and 24 of study treatment.

Table 19 Study Interruption: Schedule of Assessments – Dose Expansion Monotherapy and Combination Therapy Cohort

	Alternate Approach(es)	Treatment[a]																Pembrolizumab Monotherapy	EOT[s]
		Cycle 1						Cycle 2						Cycles 3 to 4[b]		Cycles 5 to 6[c]		Doses 5 to 17[d]	
Visit Days		1	2	4	8	15	22	1	2	4	8	15	22	1	15	1	15	Every 6 weeks	
Window(days)		0	0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	+ 7
Physical Examination[e]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI	X[e]	X	X[z]	X	X	X	X[e]	X	X[z]	X	X	X	X[e]	X	X[e]	X	X[e]	X[e]
Vital Signs[f]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI	X	X	X[z]	X	X	X	X	X	X[z]	X	X	X	X	X	X	X	X[f]	X
ECOG Performance	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained remotely via telemedicine visit or at local facility and results submitted to PI	X[g]	X		X	X	X	X[g]	X		X	X[h]	X	X[g,h]	X[h]	X[g,h]	X[h]	X[g,h]	X

Table continued on next page

	Alternate Approach(es)	**Treatment[a]**																**Pembrolizumab Monotherapy**	**EOT[s]**
		Cycle 1						**Cycle 2**						**Cycles 3 to 4[b]**		**Cycles 5 to 6[c]**		**Doses 5 to 17[d]**	
Visit Days		1	2	4	8	15	22	1	2	4	8	15	22	1	15	1	15	Every 6 weeks	
Window(days)		0	0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	+ 7
12-Lead ECG[i]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI. If cannot be performed, Astellas medical monitor to assess for study continuation.	X[i]						X[i]						X[i]		X[i]			X
Prior and Concomitant Medications	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained remotely via telemedicine visit	X	X	X[z]	X	X	X	X	X	X[z]	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 clinic and result submitted to PI	X[j]						X[j]						X[j]		X[j]		X[j]	X

Table continued on next page

	Alternate Approach(es)	Treatment[a]																Pembrolizumab Monotherapy	EOT[s]
		Cycle 1						Cycle 2						Cycles 3 to 4[b]		Cycles 5 to 6[c]		Doses 5 to 17[d]	
Visit Days		1	2	4	8	15	22	1	2	4	8	15	22	1	15	1	15	Every 6 weeks	
Window(days)		0	0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	+ 7
Clinical Laboratory Tests (chemistry, hematology, urinalysis)[j,k]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI	X[g]	X		X	X	X	X[g]	X		X	X[h]	X	X[g,h]	X[h]	X[g,h]	X[h]	X[g,h]	X
Coagulation Profile (PT/INR, fibrinogen)[k]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI	X[g]	X		X	X	X	X[g]	X		X	X[h]	X	X[g,h]	X[h]	X[g,h]	X[h]	X[g,h]	X
Thyroid Profile Panel[k,l]	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained at local facility and results submitted to PI											X		Every 6 weeks after C2D15 dose					X
PGx[m]	None	X[m]																	
Buccal Swab for HLA Typing	None	X[g]																	

Table continued on next page

	Alternate Approach(es)	**Treatment[a]**																**Pembrolizumab Monotherapy**	**EOT[s]**
		Cycle 1						**Cycle 2**						**Cycles 3 to 4[b]**		**Cycles 5 to 6[c]**		**Doses 5 to 17[d]**	
Visit Days		1	2	4	8	15	22	1	2	4	8	15	22	1	15	1	15	Every 6 weeks	
Window(days)		0	0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	+ 7
AE/SAE Assessment	Except for ASP0739 and/or Pembrolizumab administration days at study site, may be obtained remotely via telemedicine visit	X	X	X[z]	X	X	X	X	X	X[z]	X	X	X	X	X	X	X	X	X
Pharmacokinetic: ASP0739[n]	None	See Table 5 for sample time points																	
Pharmacokinetic: Pembrolizumab[n]	None	See Table 5 for sample time points																	
Anti-NY-ESO-1 antibody	None	X[g]						X[g]						X[g]		X[g]		X[t]	X
Immune Response Biomarker (ELISpot)	None	X[g]			X	X		X[g]			X	X[h]		X[g,h]	X[h]	X[g,h]	X[h]	X[h,t]	X
Immune Response Biomarker (Tetramer)	None	X[g]				X		X[g]				X[h]		X[g,h]	X[h]	X[g,h]	X[h]	X[h,t]	X
Immune Cell Phenotyping	None	X[g]			X	X		X[g]			X	X[h]		X[g,h]	X[h]	X[g,h]	X[h]	X[h,u]	X
Cytokines	None	X[g]	X	X	X	X		X[g]	X	X	X	X[h]		X[g,h]	X[h]	X[g,h]	X[h]	X[h,u]	X

Table continued on next page

	Alternate Approach(es)	Treatment[a]																Pembrolizumab Monotherapy	EOT[s]
		Cycle 1						Cycle 2						Cycles 3 to 4[b]		Cycles 5 to 6[c]		Doses 5 to 17[d]	
Visit Days		1	2	4	8	15	22	1	2	4	8	15	22	1	15	1	15	Every 6 weeks	
Window(days)		0	0	± 1	± 1	± 1	± 1	± 1	0	± 1	± 1	± 1	± 1	± 3	± 1	± 3	± 1	± 3	+ 7
Circulating tumor DNA	None	X[g]						X[g]						X[g]		X[g]		X	X[v]
Archival Tumor Tissue[o]	None	X																	
Tumor Tissue, Fresh Biopsy	None	X[q]										X[r]							
Pulmonary function test	May be obtained at local facility and results submitted to PI													X[y]				X[y]	
Radiographic Disease Assessment[p]	May be collected locally and send to PI. Assessment to be done per protocol requirements. Outside of the window assessments need to be escalated to Astellas medical monitor	Every 56 ± 7 days																	
ASP0739 Dosing	None	X						X						X		X			
Pembrolizumab Dosing[w]	Every other dose may be administered locally during Pembrolizumab monotherapy only, otherwise must be administered at study site.	X										X		Every 6 weeks after C2D15 dose				X	

Footnotes appear on next page

AE: adverse event; C: cycle; CR: complete response: CT: computed tomography; D: day; ECG: electrocardiogram; ECHO: echocardiogram; 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; MUGA: multiple gated acquisition scan; NY-ESO-1: New York esophageal squamous cell carcinoma 1; 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

a. Cycles 1 through 6 represent ASP0739 single agent or combination of ASP0739 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 ASP0739 as decided by the investigator.
c. After the first 4 cycles, participants who achieve PR or SD may continue further treatment of ASP0739 in cycles 5 and 6. Participants who reach CR will not receive additional doses of ASP0739.
d. Participants in combination therapy only will continue to receive pembrolizumab as monotherapy for doses 5 up to 17. If participant receives at least one dose of ASP0739 but discontinues combination treatment of ASP0739 at any time prior to C5D15, then the participant may continue pembrolizumab as monotherapy for up to 96 weeks for a total of 17 doses of pembrolizumab total for the study.
e. Height measurement performed at screening only. If height cannot be measured at the screening visit, it can be collected at any time during the course of the study, but should be recorded for the screening visit. Weight measurement performed at screening and day 1 of each cycle.
f. The following vital sign assessments schedules apply:
    - At C1D1 and any visit when pembrolizumab and ASP0739 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 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 ASP0739 infusion, every 15 min (-5 to +10 min window) during ASP0739 infusion, at the end of ASP0739 infusion (-5 to +10 min window), and post dose (+30 min, +1, +2, +3 and +4 hours [± 10 min window each] from end of ASP0739 infusion).
    - ASP0739 dosing only: vital signs will be obtained within 15 min prior to start of ASP0739 infusion, every 15 min (-5 to +10 min window) during ASP0739 infusion, at the end of ASP0739 infusion (-5 to +10 min window) and 30 min (± 10 min) after completion of the ASP0739 infusion. If participants are still available, additional optional vital sign assessments 3 hours (± 10 min) and 4 hours (± 10 min) after completion of the ASP0739 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 pembrolizumab infusion; at the end of pembrolizumab infusion (-5 to +10 min window), as well as, at 30 min (± 5 min), 1 hour (± 10 min) and 2 hours (± 10 min) after completion of the pembrolizumab infusion for participants in the combination therapy.
g. Obtain predose.
h. Obtain predose if participant receives pembrolizumab at the same visit.
i. 12-lead ECGs will be recorded in triplicate (at least 2 min apart per time point) and read locally. On IP administration days, ECG will be obtained:
    - At C1D1 and any visit when pembrolizumab and ASP0739 are administered together: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of ASP0739.
    - ASP0739 dosing only: ECGs are obtained predose (-1 h from start of ASP0739 infusion) and 1 to 2 h post dose of ASP0739.
    - Pembrolizumab dosing only: ECGs are obtained predose (-1 h from start of pembrolizumab infusion) and 1 to 2 h post dose of pembrolizumab.

Footnotes continued on next page

j. Urine or serum pregnancy test will be performed in women of childbearing potential. 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. For participants in combination therapy arm, troponin levels will be obtained at screening; thereafter, weekly for 6 weeks and subsequently every second week for 6 weeks.

l. Thyroid panel including triiodothyronine or free triiodothyronine, free thyroxine and thyroid stimulating hormone will be measured prior to receiving pembrolizumab for participants in the combination cohort (Screening, C2D15 then every 6 weeks).

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

n. See Table 5 for collection schedule for ASP0739 single agent and ASP0739 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. Imaging will occur every 56 ± 7 days until confirmed progression by iRECIST.

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).

s. The EOT visit will occur within 7 days of the PI decision to discontinue the participant for treatment or at the start of new anticancer treatment, whichever occurs first.

t. Samples collected at pembrolizumab doses 5, 7, 9, 11 and 13 only.

u. Samples collected at pembrolizumab doses 5 and 7 only.

v. Sample collected at the time of discontinuation due to disease progression.

w. In the combination therapy arm, pembrolizumab will be administered as an intravenous infusion over 30 min followed by ASP0739 administration at least 1 hour after pembrolizumab administration. For participants enrolled in Japanese safety lead-in, C1D8 assessments should be performed prior to discharge from hospital.

x. If participant is completing all assessments within cycle 6, EOT assessment will be on C6D22 (± 3 days) or prior to the initiation of new anticancer therapy, whichever occurs first.

y. Only participants in the combination therapy arm need to undergo pulmonary function tests at screening and at weeks 12 and 24 of study treatment.

z. These assessments only apply to the Japanese participants.

Table 20 Study Interruption: Schedule of Assessments – Schedule of Assessments for Follow-up Periods

Visit	Alternate Approach(es)	Safety Follow-up			Follow-up Period Year 1[a]	Survival Follow-up
		30 day[b]	60 day[b]	90 day[b]	Every 8 weeks[c]	Every 3 months
Window (days)		± 3	± 3	± 3	± 7	± 7
Physical Examination	May be obtained at local facility and results submitted to PI	X	X	X		
Vital Signs	May be obtained at local facility and results submitted to PI	X	X	X		
ECOG Performance	May be obtained remotely via telemedicine visit or at local facility and results submitted to PI	X	X	X		
Concomitant Medications	May be obtained remotely via telemedicine visit	X	X	X		
12-Lead ECG	May be obtained at local facility and results submitted to PI	X	X	X		
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)	May be obtained at local facility and results submitted to PI	X	X	X		
Pregnancy Test for WOCBP	May be obtained at local facility and results submitted to PI	X	X	X		
AE/SAE Assessment	May be obtained remotely via telemedicine visit	X	X	X		
Pharmacokinetic sample for cell kinetics (ASP0739)	None	See Table 5 for sample time points				
Blood Sample for NY-ESO-1 antibody	None	X	X	X	X[d]	
Blood Sample for Immune Response Biomarker (ELISpot)	None	X	X	X	X[e]	
Blood Sample for Immune Response Biomarker (Tetramer)	None	X	X	X	X[d]	
Blood Sample for Immune Cell Phenotyping	None	X	X	X	X[e]	
Blood Sample for Cytokines	None	X	X	X	X[e]	
Blood Sample for ctDNA	None	X	X	X	X[f]	

Table continued on next page

Visit	**Alternate Approach(es)**	**Safety Follow-up**			**Follow-up Period Year 1[a]**	**Survival Follow-up**
		30 day[b]	60 day[b]	90 day[b]	Every 8 weeks[c]	Every 3 months
Window (days)		± 3	± 3	± 3	± 7	± 7
Radiographic Disease Assessment	Assessment to be done per protocol requirements and submitted to PI. Outside of the window assessments need to be escalated to Astellas medical monitor	Every 56 ± 7 days				
Survival Follow-up[g]	May be obtained remotely via telemedicine visit					X

AE: adverse event; ctDNA: circulating tumor DNA; ECG: electrocardiogram; ECOG: eastern cooperative oncology group; ELISpot: enzyme-linked immunospot; EOT: end of treatment; NY-ESO-1: New York esophageal squamous cell carcinoma 1; PI: principal investigator; SAE: serious adverse event; WOCBP: woman of childbearing potential

a. Follow-up visits every 2 months or until progression or start of a new anticancer therapy or death (whichever occurs first).
b. From the last dose.
c. From EOT or the last planned assessment if EOT was not performed.
d. Maximum of 5 samples collected during Follow-up Period Year 1. Samples will be collected at the time of the disease assessment visit.
e. Maximum of 1 sample collected during Follow-up Period Year 1. Sample will be collected at the time of the disease assessment visit.
f. Sample will be collected at the time of discontinuation due to disease progression or the start of a new anticancer therapy.
g. Outcomes will be assessed by telephone calls every 3 months for up to 12 months.

Table 21 Study Interruption: Schedule of Assessments – Schedule of Replication Competent Lentivirus for Dose Escalation Cohort, Dose Expansion Cohort and Safety Lead-in Cohort

Assessment	Alternate Approach(es)	C1D1	3 Months after Treatment Initiation or End of Treatment, whichever is first	6 Months after Treatment Initiation	12 Months after Treatment Initiation	18 Months after Treatment Initiation
Window		0	± 7 day	± 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.

b. Obtained predose.

INVESTIGATIONAL PRODUCT SUPPLY

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

- Increase stock of IP on site to reduce number of shipments required, if site space will allow.

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
α-GalCer	α Galactosylceramide
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-PD-1	anti-programmed cell death protein 1
APGD	Astellas Pharma Global Development, Inc.
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
C	cycle
C_{max}	maximum concentration
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CRO	contract research organization
CRS	cytokine-release syndrome
CSR	clinical study report
CT	computed tomography
CTA	cancer testis antigens
CTCAE	common terminology criteria for adverse events
ctDNA	circulating tumor DNA
C_{trough}	concentration immediately prior to dosing at multiple dosing
CV	coefficient of variation
DCR	disease control rate per RECIST v1.1
DEAS	DLT evaluation analysis set
DESC	Dose Escalation and Safety Committee
DLT	dose limiting toxicity
DOR	duration of response per RECIST v1.1
DPD	Data Protection Directive
ECG	electrocardiogram

Abbreviations	Description of abbreviations
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European Economic Area
ELISpot	enzyme-linked immunospot
EOT	end of treatment
ESCC	esophageal squamous cell carcinoma
FAS	full analysis set
FFPE	formalin-fixed, paraffin embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
HEK293	human embryonic kidney cell
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	confirmed disease progression by iRECIST
iCR	complete response based on iRECIST
iDCR	disease control rate per iRECIST
iDOR	duration of response per iRECIST
IEC	Independent Ethics Committee
IFNg	interferon gamma
ILD	interstitial lung disease
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
LA-CRF	liver abnormality case report form
LFT	liver function test
MRCL	myxoid/round cell liposarcoma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

Abbreviations	Description of abbreviations
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NK	natural killer
NKT	natural killer T
NSCLC	non-small cell lung cancer
NY-ESO-1	New York esophageal squamous cell carcinoma 1
ORR	objective response rate per RECIST v1.1
OS	overall survival
PD	progressive disease
PDAS	pharmacodynamic analysis set
PFS	progression-free survival per RECIST v1.1
PGx	pharmacogenomic
PKAS	pharmacokinetic analysis set
PMDA	Pharmaceutical and Medical Devices Agency
PR	partial response
PT/INR	prothrombin time/international normalized ratio
PV	pharmacovigilance
QA	quality assurance
QC	quality control
QTL	quality tolerance limits
R/R	relapsed/refractory
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
SAP	statistical analysis plan
SD	stable disease
SOC	standard of care
SOP	standard operating procedure
SS	synovial sarcoma
SUSAR	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TEM	Tolerability Evaluation Meeting
t_{max}	time of maximum concentration
ULN	upper limit of normal
USM	urgent safety measure
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 pharmacogenomics).
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.

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12 PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol 0739-CL-0101 A Phase 1/2 Open-label Study Investigating the Safety, Tolerability and Efficacy of ASP0739 as a Single Agent and in Combination with Pembrolizumab in Patients with Advanced Solid Tumors known to Express NY-ESO-1

Amendment 4 [Substantial] 24 Aug 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

This amendment is to update the protocol for accuracy, to provide clarification and to add responses to requests from the PMDA.

Summary of Changes

Table 1 Substantial Changes

Section Number	Description of Change	Brief Rationale
1.1, 1.2, 2.3.2, 4.1, 6.3.1, 10.1.5.1	Add phase 2 single agent dose expansion cohort with Japanese safety lead-in and a TEM	To update the protocol to reflect the decision to include the Japanese safety lead-in cohort
1.3 (Table 2), 10.12 (Table 19)	Footnote “i", which specified which participants should undergo ECHO or MUGA assessment, is removed	ECHO (or MUGA) assessments will now be conducted for all participants in combination therapy arms as part of screening
1.3 (Table 5)	Table headers are updated and footnotes added	To reflect inclusion of the Japanese safety lead-in participants
5.1	Revised inclusion criterion 17 to read “Participant has measurable disease according to RECIST 1.1. For participant with only 1 measurable lesion and prior radiotherapy, the lesion must be outside the field of prior radiotherapy or must have documented progression following radiation therapy.”	To clarify inclusion criterion 17 regarding history of prior radiotherapy
5.2	Allow participants who have received systemic immunomodulators in the dose escalation phase and systemic immunomodulators for NY-ESO-1 solid tumor cohorts in the dose expansion phase in exclusion criterion 2	To clarify exclusion criterion 2 regarding prior use of systemic immunomodulators in both the dose escalation and dose expansion phases

Section Number	Description of Change	Brief Rationale
5.2	Add suspected hypersensitivity to bovine-derived protein or any ingredients of ASP0739 as a new exclusion criterion	Added as a safety precaution

Table 2 Nonsubstantial Changes

Section Number	Description of Change	Brief Rationale
Contact Details of Sponsor's Key Personnel and 13	Update identity of medical monitor to PPD and correct contact information	To align with updated personnel
1.1 and 4.1	Clarify that participant replacement includes participants in the safety lead-in	To provide clarification
1.1, 4.1 and Table 8	Remove "Part 1"	To correct an error
1.1, 4.1, 4.4, 10.5.2	Clarify IP includes ASP0739 and pembrolizumab	To provide clarification
1.2 (Figure 2)	Provide clarity for study design in footnotes	To provide clarification
1.3 (Table 1), 10.12 (Table 18)	An "X" was added to C2D2 for ECOG performance	To correct an error
1.3 (Table 1 and Table 2), 10.12 (Table 18 and Table 19)	Timing of sampling for thyroid function assessments is modified	To align with sampling schedules from other programs
1.3 (Table 2), 10.12 (Table 19)	Clarify pulmonary function testing during C1 and clarify ECOG, clinical laboratory, coagulation and thyroid panel, immune response biomarker, immune cell phenotyping and cytokine assessment times relative to dosing	To provide clarification
1.3 (Table 3), 10.12 (Table 20)	Clarify the timing of the last planned assessment	To provide clarification
2.3.1.1, 4.3.1	Update risk assessment and dose rationale for ASP0739	To provide more current information

Section Number	Description of Change	Brief Rationale
4.1	Remove "at least possibly related to study drug" from grade ≥ 3 liver function test abnormality and "treatment-related" from the description of grade 5 toxicity	To provide clarification
4.1	The far-right column is removed from 2 tables describing "Number of Participants Treated at Current Dose Level"	Columns are removed because the number of participants noted, 9, will not be enrolled
5.2	Criterion 16 is removed and placed as criterion 4 in the subsequent section entitled "Additional Exclusion Criteria for Participants in Combination Therapy Cohorts"	Criterion was placed in the incorrect location; to correct an error
Table 1, Table 2, 7.2.4	Update timing of ECG assessments relative to IP dosing	To provide clarification
7.5.2	Add that participants who have an FFPE block and a frozen tissue specimen taken within 56 days prior to the first dose of study treatment do not require a new biopsy	To improve the participant experience
7.8	Modify text related to total amount of blood collected	To clarify the maximum amount of blood collected at any one visit and over the course of any cycle
10.1.12	Replace QTL text in Quality Assurance section with bullet point from current template	To reflect the current protocol template version
10.6 (Table 13)	Include CO_2 as an option for chemistry testing in clinical laboratory tests and make the test not mandatory if testing is not available	To provide clarification
10.6 (Table 13)	Add that the thyroid panel is for the combination cohort only	To provide clarification
Throughout	Minor administrative-type changes, e.g., typos, format, numbering, consistency throughout the protocol.	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	
PPD	Data Science
PPD	

Global Protocol Format v9.0