An Open-label, Multicenter, Multicohort, Phase 2 Study to Evaluate Enfortumab Vedotin in Subjects with Locally Advanced or Metastatic Malignant Solid Tumors (EV-202)

ISN/Protocol 7465-CL-202

Amendment 6 [Nonsubstantial]

05 Feb 2024

IND 116360

Sponsor:

Astellas Pharma Global Development Inc.

Northbrook, IL 60062, US

Protocol History:

Version 1.0 [25 Nov 2019]

Amendment 1 [17 Feb 2021]

Amendment 2 [21 Oct 2021]

Amendment 3 [31 Mar 2022]

Amendment 4 [14 Feb 2023]

Amendment 5 [13 Apr 2023]

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SIGNATURES

1. 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. 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].

3. INVESTIGATOR'S SIGNATURE

An Open-label, Multicenter, Multicohort, Phase 2 Study to Evaluate Enfortumab Vedotin in Subjects with Locally Advanced or Metastatic Malignant Solid Tumors (EV-202)

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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: _____ _____

Address: _____

_____

CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL

24-hour Contact for Serious Adverse Events See [Section 12.4.5 Reporting Procedures for Serious Adverse Events]	**Please fax or email the serious adverse events/special situations worksheet to:** Astellas Pharma Global Development Inc. Global 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** **For Japan:** Astellas Pharma Inc. – Japan Pharmacovigilance Fax number: +81-(0)3-3243-5747 Email: rk-safety-jp@jp.astellas.com
Parexel Medical Monitor/Study Physician	PPD PAREXEL International PPD
Astellas Medical Expert	PPD Astellas Pharma Global Development Inc. PPD
Clinical Research Contacts	PPD Astellas Pharma Global Development Inc.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 5/Version 6 [Substantial]	13 Apr 2023
Amendment 4/Version 5 [Substantial]	14 Feb 2023
Amendment 3/Version 4 [Substantial]	31 Mar 2022
Amendment 2/Version 3 [Substantial]	21 Oct 2021
Amendment 1/Version 2 [Substantial]	17 Feb 2021
Original Protocol/Version 1	25 Nov 2019

Amendment 6/Version 7 [Nonsubstantial] 05 Feb 2024

This amendment is considered to be nonsubstantial 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 and EU Clinical Trial Regulation because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

Global update for management of pneumonitis/interstitial lung disease (ILD) related to enfortumab vedotin and additional clarifications related to Cohort 9.

Summary of Changes

Nonsubstantial Changes

Section Number	**Description of Change**	**Brief Rationale**
CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL	Update Clinical Research Contacts.	Update contact details of sponsors key personnel.
1.1, 6.5	Change second level bullet under cohort 9 to delete "~~Other glucocorticoid use except when used for the following purposes:~~" and "~~Note: Inhaled steroids are allowed for management of asthma.~~", while retaining and revising third level bullets to second level bullets.	Clarification of glucocorticoid use in Cohort 9.
1.1, 4.1	Add "**(both enfortumab vedotin and pembrolizumab)"** to "Subjects in cohort 9 who discontinue study treatment …)."	Clarify that study treatment is considered to be both enfortumab vedotin and pembrolizumab.
1.2 (Figure 2)	Remove pre-screening consent/prescreening process for Cohort 9.	Pre-screening and main informed consent form (ICF) language was combined into one consent form; therefore, the schedule of assessments

Section Number	Description of Change	Brief Rationale
		was updated to remove pre-screening consent/pre-screening process.
1.2 (Figure 2)	Update Cohort 9 schema to remove upper Pre-screening box. Replace "N~~o local PD-L1 result~~" and "L~~ocal PD-L1 result available~~" with "**PD-L1 Testing (Local or Central)**" in the Screening/Baseline Period.	Update to align with removal of the Pre-screening consent/pre-screening process.
1.3 (Table 1, Table 2)	Merge Pregnancy Test at Follow-up (30-day Safety Follow-up, Post Treatment Follow-up, and Long-term Follow-up) and replace "X" with "**Pregnancy test monthly until 6 mo after last dose of study treatment**."	Clarify timing of Pregnancy Test.
1.3 (Table 1, Table 2)	Remove footnotes (Table 1: ~~12,13~~; Table 2: ~~14,15)~~ for 12-lead ECG at Screening/Baseline cycle Day -7 to -1.	Updated to remove footnotes for clinical laboratory assessments from the 12-lead ECG assessment.
1.3 (Table 2)	Change Treatment Subsequent Every Cycle at Cycle 1 from a Visit Window of ~~±2~~ to **±3**.	Update timing of Visit Window to align with cohorts 1-8.
1.3 (Table 2)	Update Prior/Concomitant Medication and AE Assessments at Follow-up to extend to 30-day Safety Follow-up.	Update to align with cohorts 1-8 as originally intended.
1.3 (Table 2)	Remove footnote 15 from Hemoglobin A1c.	Removed duplicate information.
1.3 (Table 2)	Move the assessments of Informed Consent, Tumor Tissue Sample, and PD-L1 Test Result from Pre-Screening to Screening.	Update to align with removal of the Pre-screening consent/pre-screening process.
1.3 (Table 2)	Merge adverse events (AE) and Prior ConMed rows so that "Every visit" starts at Screening/Baseline.	Correct formatting in the schedule of assessment.
1.3 (Table 2, footnote 10), 7.1.1	Remove bone imaging as a requirement at screening assessment for Cohort 9.	Bone imaging is not routine standard of care in HNSCC, and the CT scan can assess for metastasis to some extent.
1.3 (Table 2, footnote 11), 4.1, 7.1.1	Revise 36 days to **42** days in the disease assessment "every 6 weeks (~~36~~**42** days ±7 days) throughout the study."	Correction of Cohort 9 scan window from 36 to 42 days.
1.3 (Table 2, footnote 12)	Add "**iRECIST should be assessed in parallel with all RECIST 1.1 assessments at every timepoint.**"	Clarify that iRECIST will be assessed in parallel with RECIST at every timepoint.

Section Number	Description of Change	Brief Rationale
1.3 (Table 2, footnote 17)	Add "**cycle 2"** to the required thyroid function tests treatment period.	Correct omission of Cycle 2 from footnote.
6.4	Add overdose definition for pembrolizumab.	Clarification of dosing noncompliance for enfortumab vedotin and pembrolizumab.
7.3.6, 12.5	Add Japan country specific applicable assessment forms for collection of non-serious and SAEs.	Update based on Japan specific amendment.
6.6.1	Add "**Participants who experience an unacceptable AE that is clearly attributable only to pembrolizumab may continue on enfortumab vedotin monotherapy until a discontinuation criterion is met.**"	Clarify dose interruptions vs discontinuation guidance, interrupting/discontinuing one drug vs both drugs.
6.6.1.2	Add further guidance on the management of pneumonitis/ILD related to enfortumab vedotin.	Update management of pneumonitis/ILD related to enfortumab vedotin.
6.6.2.1	Add "**Participants who experience unacceptable toxicity that is clearly attributable only to enfortumab vedotin may continue on pembrolizumab monotherapy up to a maximum of 35 cycles.**"	Clarify dose interruptions vs discontinuation guidance, interrupting/discontinuing one drug vs both drugs.
7.7	Add maximum amount of blood collection for cohorts 1-8 and cohort 9.	Clarify maximum volume of blood collection for each cohort.
8.1	Update dose discontinuation guidance to "**clearly**" attributable to either pembrolizumab or enfortumab vedotin treatment.	Clarify dose discontinuation guidance for discontinuing one drug vs both drugs.
10.1	Update monitoring to indicate the study does not perform 100% source data validation	Clarify monitoring source data validation.
Throughout	Minor administrative-type changes were made, e.g., typos, formatting, section and footnote numbering and other continuity throughout the protocol.	To provide clarification and proper interpretation of the protocol.

1 PROTOCOL SUMMARY

1.1 Synopsis

Date and Version of Protocol Synopsis:	Amendment 6
Sponsor: Astellas Pharma Global Development Inc. (APGD) **Collaborator:** Seagen, Inc.	**Protocol Number:** 7465-CL-202
Compound Name: Enfortumab vedotin (ASG-22CE)	**Phase of Development:** Phase 2
Title of Study: An Open-label, Multicenter, Multicohort, Phase 2 Study to Evaluate Enfortumab Vedotin in Subjects with Locally Advanced or Metastatic Malignant Solid Tumors (EV-202)	
Planned Study Period: From approximately 1Q2020 to 1Q2026	

Study Objective(s) and Endpoint(s):

Cohorts 1 to 8:

Objective(s)	Endpoint(s)
Primary	
• To determine the antitumor activity of enfortumab vedotin as measured by confirmed objective response rate (ORR) per investigator assessment	• Confirmed ORR (complete response [CR] + partial response [PR]) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as determined by investigator
Secondary	
• To assess other measures of antitumor activity of enfortumab vedotin per investigator assessment	• Duration of response (DOR) per RECIST Version 1.1 per investigator assessment • Disease control rate (DCR) (CR + PR + stable disease [SD]) per RECIST Version 1.1 per investigator assessment • Progression-free survival (PFS) per investigator assessment
• To assess the overall survival (OS)	• OS
• To assess the safety and tolerability of enfortumab vedotin	• Safety variables o Adverse events (AEs) o Laboratory tests o Vital sign measurements o 12-lead electrocardiogram o Eastern Cooperative Oncology Group (ECOG) performance status

Exploratory	
• To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome, including Nectin-4 expression • To assess the pharmacokinetics of enfortumab vedotin and monomethyl auristatin E (MMAE) • To assess the immunogenicity of enfortumab vedotin • To evaluate the treatment effect of enfortumab vedotin on quality of life (QOL) • To assess measures of antitumor activity of enfortumab vedotin per blinded independent central review (BICR)	• Exploratory genomic and/or other biomarkers that may correlate with treatment outcome, including Nectin-4 expression • Selected pharmacokinetic parameters of enfortumab vedotin and MMAE • Incidence of antitherapeutic antibodies (ATA) to enfortumab vedotin • Patient reported outcome (PRO) per EuroQOL 5-dimensions (EQ-5D-5L) and global pain assessment (worst pain in the last 24 hours) • Response related endpoints per BICR

Cohort 9:

Objective(s)	**Endpoint(s)**
Primary	
• To determine the antitumor activity of enfortumab vedotin in combination with pembrolizumab	• Confirmed ORR (CR + PR) per RECIST Version 1.1 as determined by investigator
Secondary	
• To assess other measures of antitumor activity of enfortumab vedotin in combination with pembrolizumab per investigator assessment	• DOR per RECIST Version 1.1 by investigator assessment • DCR (CR + PR + SD) per RECIST Version 1.1 by investigator assessment • PFS per RECIST Version 1.1 by investigator assessment
• To assess the OS of enfortumab vedotin in combination with pembrolizumab	• OS
• To assess the safety and tolerability of enfortumab vedotin in combination with pembrolizumab	• Safety variables o AEs o Laboratory tests o Vital sign measurements o 12-lead electrocardiogram o ECOG performance status
Exploratory	
• To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome, including Nectin-4 expression	• Exploratory genomic and/or other biomarkers that may correlate with treatment outcome, including Nectin-4 expression
• To assess the pharmacokinetics of enfortumab vedotin and MMAE	• Selected pharmacokinetic parameters of enfortumab vedotin and MMAE

• To assess the immunogenicity of enfortumab vedotin	• Incidence of ATA to enfortumab vedotin
• To evaluate the treatment effect of enfortumab vedotin in combination with pembrolizumab on QOL	• PRO per EORTC QLQ H&N43, global pain assessment (worst pain in the last 24 hours), FACT-G question G05 and symptom-specific questions from PRO-CTCAE
• To assess measures of antitumor activity of enfortumab vedotin in combination with pembrolizumab per BICR	• ORR, DOR, DCR and PFS per RECIST Version 1.1 by BICR
• To assess measures of antitumor activity of enfortumab vedotin in combination with pembrolizumab per modified RECIST v1.1 for immune-based therapeutics (iRECIST)	• ORR, DOR, DCR and PFS per iRECIST by investigator assessment

Planned Total Number of Study Sites and Location(s):

Approximately 50 study sites globally

Study Population:

Subjects with locally advanced or metastatic malignant solid tumors, including:

- Hormone receptor positive/ human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer
- Triple negative breast cancer (TNBC)
- Squamous non-small cell lung cancer (Squamous NSCLC)
- Non-squamous non-small cell lung cancer (Non-squamous NSCLC)
- Head and neck cancer
- Gastric cancer and esophageal adenocarcinoma (EAC) including gastroesophageal junction (GEJ) adenocarcinoma
- Esophageal squamous cell carcinoma (ESCC)
- Head and neck squamous cell carcinoma (HNSCC)

Number of Subjects to be Enrolled/Randomized:

Approximately 320 subjects with malignant solid tumors in 8 cohorts; approximately 40 subjects in each cohort

Study Design Overview:

This is an open-label, multicenter, multicohort, phase 2 study designed to assess the antitumor activity and safety of enfortumab vedotin as a single agent (cohorts 1 to 8) and in combination with pembrolizumab (cohort 9) in adult subjects who have locally advanced or metastatic malignant solid tumors. Approximately 40 subjects will be enrolled into each of the following cohorts.

- Cohort 1: HR+/HER2- breast cancer; or
- Cohort 2: TNBC; or
- Cohort 3: Squamous NSCLC; or
- Cohort 4: Non-squamous NSCLC; or
- Cohort 5: Head and neck cancer; or
- Cohort 6: Gastric or GEJ or esophageal cancer (reallocated to cohorts 7 or 8)
- Cohort 7: Gastric and EAC including GEJ adenocarcinoma
- Cohort 8: ESCC
- Cohort 9: First-line HNSCC

For each cohort, one interim analysis is planned to assess the antitumor activity for that cohort. The interim analysis will be performed for a given cohort at the time when 20 subjects are evaluable for tumor response per investigator assessment following study treatment. A Bayesian optimal design for phase 2 (BOP2) [Zhou et al, 2017] is used to guide interim decision rule. For each cohort, based on the 2-stage BOP2 design, when the number of subjects with confirmed

response (CR and PR) is less than the prespecified minimum number of responders at stage 1, the enrollment of the cohort may stop; otherwise, the enrollment will continue into Stage 2 until the planned size of the cohort is reached.

In cohorts 1 to 8, subjects will receive enfortumab vedotin at a dose of 1.25 mg/kg as an intravenous (IV) infusion on days 1, 8 and 15 of each 28-day cycle.

In cohort 9, subjects will receive enfortumab vedotin 1.25 mg/kg on days 1 and 8 and pembrolizumab 200 mg on day 1 of each 21-day cycle.

For each subject, the study will consist of 3 periods: screening/baseline, treatment and follow-up.

The screening/baseline period will take place up to 28 days prior to the first dose of study treatment. For cohort 9, a local programmed death-ligand 1 (PD-L1) test result may be used for eligibility. A PD-L1 combined positive score (CPS) ≥ 1 is required for enrollment. An archival tumor sample will be submitted from each subject for central PD-L1 and other biomarker testing. If archival tumor tissue for central PD-L1 testing is insufficient or not available, a biopsy will be performed to obtain a tumor sample for central testing.

In the treatment period, starting at cycle 1, subjects in cohorts 1 to 8 will receive enfortumab vedotin on days 1, 8, and 15 every 28-day cycle until one of the treatment discontinuation criteria are met. Subjects in cohort 9 will receive enfortumab vedotin on days 1 and 8 and pembrolizumab on day 1 of each 21-day cycle until a discontinuation criteria is met.

For cohorts 1 to 8, imaging scan and disease assessment will be performed at screening/baseline and repeated every 8 weeks (56 days ± 7 days) from the first dose of study treatment throughout the study until the subject has radiologically-confirmed disease progression, initiates a new subsequent anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first. After 1 year on study treatment, the frequency of disease assessment will be reduced to every 12 weeks (84 days ± 7 days). Subjects in cohorts 1 to 8 who discontinue study treatment for reasons other than radiologically-confirmed disease progression by RECIST Version 1.1 will enter into a post treatment follow-up period and continue to receive imaging scans every 8 weeks (56 days ± 7 days) until the subject has radiologically-confirmed disease progression, initiates a new anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first.

In cohort 9, the first on-study imaging will be performed 9 weeks (± 7 days) from the first dose of study treatment and then every 6 weeks (± 7 days) throughout the study until the subject has radiologically-confirmed disease progression (confirmed progressive disease [iCPD] per modified RECIST v1.1 for immune-based therapeutics [iRECIST]), initiates a new subsequent anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first. After 18 months on study treatment, the frequency of disease assessment will be reduced to every 9 weeks (± 7 days). Subjects in cohort 9 with unconfirmed progressive disease per iRECIST guidelines [Seymour et al, 2017] who are clinically stable may continue on study treatment until progression is confirmed by the investigator (iCPD) at the next imaging assessment 6 weeks (± 7 days) after iUPD. Treatment with pembrolizumab will be discontinued once the subject has received a maximum of 35 administrations of pembrolizumab (approximately 2 years).

Subjects in cohort 9 who discontinue study treatment (both enfortumab vedotin and pembrolizumab) for reasons other than radiologically confirmed disease progression per iRECIST will enter into a post treatment follow-up period and have physical exams, ECOG and disease assessments every 6 weeks (± 7 days) up to 18 months after first dose, then every 9 weeks (± 7 days) until the subject has radiologically confirmed disease progression per iRECIST as determined by the investigator, initiates a subsequent anticancer therapy, dies, withdraws consent, or the study closes. During study treatment, palliative radiotherapy on a nontarget lesion that is not progressing will not be considered a subsequent anticancer therapy; however, radiotherapy on any target lesion will be a subsequent anticancer therapy.

Copies of all imaging scans will also be sent to the independent review facility in a timely manner. Images at the independent review facility will be stored. Imaging scans for a cohort may be read at the independent review facility when the minimum number of responders per investigator assessment (subjects with confirmed CR and PR) to claim promising antitumor activity at stage 1 are met based on the 2-stage BOP2 design. Central images may also be read in certain circumstances as determined by the sponsor.

After radiologically-confirmed disease progression or initiation of subsequent anticancer therapy, whichever occurs first, subjects will be contacted every 12 weeks in the long-term follow-up period for survival status until death, withdrawal of consent, lost to follow-up or study closure, whichever occurs first.

Confirmed ORR per investigator assessment is the primary endpoint. Confirmed ORR is defined as the proportion of subjects whose objective response is confirmed CR or PR according to RECIST Version 1.1. Response (CR or PR) must be confirmed with a repeat imaging scan 4 weeks (28 days + 7-day window) after first response.

Blood samples for pharmacokinetics and antitherapeutic antibodies (ATA) will be collected at protocol-specified time points. Validated assays will be used to measure the concentrations of enfortumab vedotin and MMAE in serum or plasma and to assess ATA. Samples for exploratory biomarkers will be collected at protocol-specified time points. Enfortumab vedotin biomarker assessments will not be used for subject selection.

The following are discontinuation criteria from study treatment for individual subjects:

- Subject develops documented radiological disease progression (iCPD per iRECIST in cohort 9)
- Subject starts on a new anticancer therapy
- Subject develops unacceptable toxicity
- Female subject becomes pregnant
- Investigator decides it is in the subject's best interest to discontinue
- Subject requests to stop treatment
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment
- Subject has continuous dose interruption > 6 months
- Study is terminated by sponsor

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures. Subjects may be discontinued from the study for any of the following reasons:

- Lost to follow-up
- Death
- Subject withdrawal of consent
- Study termination by sponsor

On a periodic basis, a Safety Monitoring Committee (SMC) will review the safety data of the study. The SMC may recommend whether the study should be terminated, modified or continue unchanged based on ongoing reviews of study safety data.

Investigational Product(s):

Name:

Enfortumab vedotin

Dose, Mode of Administration and Dose Modification:

Enfortumab vedotin at a dose of 1.25 mg/kg will be administered as an IV infusion on days 1, 8 and 15 of every 28-day cycle for cohorts 1 to 8 and on days 1 and 8 of every 21-day cycle for cohort 9. Enfortumab vedotin will be administered based on the subject's actual body weight on day 1 of each cycle except for subjects weighing greater than 100 kg; in such cases, the dose will be calculated based on a maximum weight of 100 kg. Enfortumab vedotin will be administered intravenously over an approximately 30-minute period.

Dose reduction to 1, 0.75 or 0.5 mg/kg will be allowed depending on the type and severity of toxicity. Subjects requiring a dose reduction may be re-escalated by 1 dose level (i.e., subjects reduced to 0.75 mg/kg may only be re-escalated to 1 mg/kg) provided the toxicity does not require study drug discontinuation and has returned to baseline or ≤ grade 1. If the toxicity recurs, re-escalation will not be permitted. Subjects with ≥ grade 2 corneal AEs will not be permitted to dose re-escalate.

Dose interruptions for any enfortumab vedotin associated toxicities are permitted at the discretion of the investigator. Dose interruptions may last up to 8 weeks (2 cycles) for subjects in cohorts 1 to 8 and up to 6 weeks (2 cycles) for subjects in cohort 9. Dose interruptions for subjects who are deriving clinical benefit from treatment may be extended beyond 8 weeks (cohorts 1 to 8) or 6 weeks (cohort 9) after consultation with the medical monitor on a monthly basis, if the subject's toxicity does not otherwise require permanent discontinuation. During dose interruptions, disease assessments must continue to be performed at the protocol-specified frequency and disease status must remain at least SD per RECIST v1.1. If dose interruption is continuous > 6 months, the subject's study treatment will be permanently discontinued.

Refer to Section 6.6.1 [Table 7] and [Table 8] for dose modification recommendations for enfortumab vedotin.

Name:

Pembrolizumab (cohort 9 only)

Dose, Mode of Administration and Dose Modification:

Pembrolizumab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, United States Pharmacopeia (USP). Pembrolizumab will be administered as a dose of 200 mg using a 30-minute intravenous infusion on day 1 of each 3-week cycle, approximately 30 minutes after completion of the enfortumab vedotin administration. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and + 10 minutes is permitted (i.e., infusion time is 30 minutes (-5 min/+10 min).

The pharmacy manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

Refer to Section 6.6.2 [Table 9] and [Table 10] for dose modification recommendations for pembrolizumab.

If the medical monitor and site investigator determine that a dose interruption for pembrolizumab is needed, an interruption of all day 1 dose of enfortumab vedotin must also occur and may last for up to 3 weeks (1 cycle). For subjects deriving benefit, interruption of pembrolizumab for longer than 3 weeks should be discussed with the medical monitor. For delays longer than 12 weeks, the medical monitor should be consulted before resuming study therapy.

Concomitant Treatment (Medication and Nonmedication Therapy) Restrictions or Requirements:

If the investigator determines that any of the following medications are necessary to provide adequate medical support to the subject, the subject must be withdrawn from further administration of the study treatment:

- Other investigational drugs
- Chemotherapy or other medications intended for antitumor activity. This does not apply to subjects on endocrine therapy, or to subjects on agents intended for the treatment of bone metastasis where subjects should be on a stable dose of bone targeting agents for at least 2 weeks prior to study entry (e.g., bisphosphonates, or receptor activator of nuclear factor kappa-B [RANK] ligand inhibitors).
- Radiation therapy except palliative radiation for nontarget lesions that is approved by the sponsor. Note: Radiation therapy to a preexisting symptomatic solitary lesion or to the bone may be considered on an exceptional case-by-case basis after consultation with the sponsor. The radiated lesion must be a nontarget lesion per RECIST Version 1.1 and the subject must have clear measurable disease outside the radiated field. Enfortumab vedotin may not be given concurrently with radiation therapy.
- Subjects who are receiving strong cytochrome P450 (CYP)3A4 inhibitors concomitantly with enfortumab vedotin should be closely monitored for adverse reactions.
- For cohort 9: Live or attenuated vaccines within 30 days prior to the first dose of study treatment and while participating in the study.
- For cohort 9: Systemic glucocorticoids except when used for the following purposes:
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - For the prevention of emesis
    - To premedicate for IV contrast allergies
    - To treat COPD exacerbations (only short-term oral or IV use in doses > 10 mg/day prednisone equivalent)
    - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease.

Duration of Treatment:

Subjects will be allowed to receive enfortumab vedotin (and pembrolizumab for cohort 9) until treatment discontinuation criteria are met.

Statistical Methods:

Sample Size Justification:

The planned sample size for cohorts 1 to 8 is 40 subjects in each cohort. Assuming the ORR of current standard of care (reference ORR for the 7 tumor types chosen for the study) ranges from 10% to 20%, and at least a 10% absolute increase in ORR is considered clinical meaningful improvement, the sample size of 40 subjects allows to have 80% confidence interval of ORR for the study drug to exclude the reference ORR.

The planned sample size for cohort 9 is 40 subjects. Assuming the reference ORR for cohort 9 is 20%, and at least a 25% absolute increase in ORR is considered clinical meaningful improvement for combination therapy, the sample size of 40 subjects allows a 92% power to detect a statistically significant difference at type 1 error rate of 1-sided 0.025.

Efficacy:

Confirmed ORR (CR+PR) and DCR (CR+PR+SD) as per RECIST Version 1.1 will be calculated and the corresponding 95% confidence intervals will be constructed based on Clopper-Pearson method for each tumor type. For cohort 9, analyses will also be calculated based on iRECIST. Other efficacy endpoints, including DOR, PFS and OS will be summarized using Kaplan-Meier method. Efficacy analysis will include all subjects who were treated and with evaluable tumor response data upon analysis cutoff date.

Safety:

The Safety Analysis Set (SAF) will be used for the safety analysis. All subjects who are enrolled and received study drug will be included in the SAF. The frequency of AEs and the serious AEs will be summarized by MedDRA system organ class (SOC) and preferred term. In addition, summary statistics will be provided for the following safety parameters:

- Laboratory values
- Vital sign measurements
- ECOG performance status

Pharmacokinetics:

Descriptive statistics (e.g., number, mean, standard deviation, minimum, median, maximum, coefficient of variation and geometric mean) will be provided for serum or plasma concentrations of enfortumab vedotin and MMAE. Additional model-based analyses and exposure response may be performed and reported separately.

Pharmacodynamics | Immunogenicity:

The ATA to enfortumab vedotin will be summarized by cycle and overall, and possible relationship to pharmacokinetics will be explored.

Exploratory Biomarkers:

Descriptive statistics will be provided for exploratory biomarker parameters whenever applicable. Analysis of the relationship between exploratory biomarker measurements and pharmacokinetics, efficacy, safety profile in subjects may be performed.

Interim Analyses:
For each cohort, one planned interim analysis will be performed to evaluate confirmed ORR at the time when 20 subjects had evaluable tumor response data per investigator assessment following study treatment. The 2-stage BOP2 design is used to guide the interim decision rule. A cohort will proceed to stage 2 when the minimum number of responders (see table below) from stage 1 has been observed; otherwise the cohort may be closed for further enrollment. The sponsor will make the final decision on stopping cohort enrollment based on the overall evaluation of antitumor activity and safety data including subject's Nectin-4 expression data.

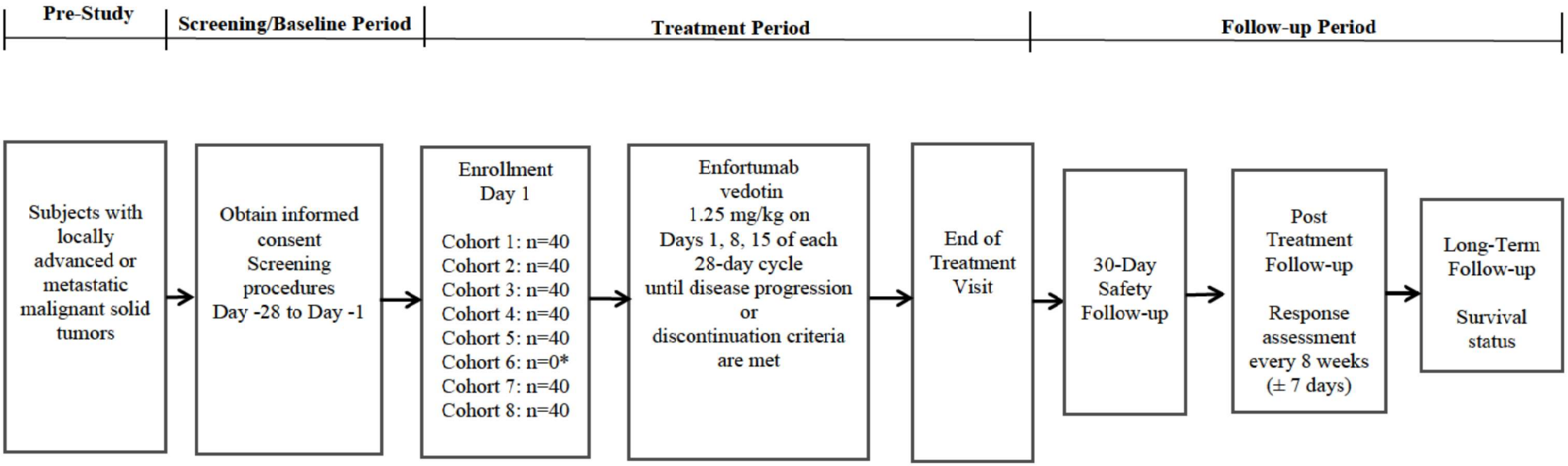
Decision Rules Based on Objective Response Rate					
Cohort	**Cancer Type**	**Number of Evaluable Subjects Planned at Interim Analysis (Stage 1)**	**Minimum Number of Responders to Proceed to Stage 2**	**Number of Evaluable Subjects at Final Analysis (Stage 2)**	**Minimum number of Responders to Claim Promising Antitumor Activity**
Cohort 1	HR+/HER2- breast cancer	20	4	40	12
Cohort 2	Triple negative breast cancer	20	3	40	10
Cohort 3	Squamous non-small cell lung cancer	20	2	40	7
Cohort 4	Non-squamous non-small cell lung cancer	20	3	40	10
Cohort 5	Head and neck cancer	20	2	40	7
Cohort 6*	Gastric or GEJ or esophageal cancer	20	2	40	7
Cohort 7	Gastric, EAC and GEJ adenocarcinoma	20	2	40	7
Cohort 8	ESCC	20	2	40	7
Cohort 9	HNSCC	20	5	40	14

EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; GEJ: gastroesophageal junction; HR+: hormone receptor positive; HER2-: human epidermal growth factor receptor 2-negative; HNSCC: head & neck squamous cell carcinoma

*All subjects initially enrolled in Cohort 6 under protocol version 1.0 and 2.0 will be reallocated to Cohort 7 or 8 based on tumor type/histology and Cohort 6 closed to further enrollment.

1.2 Study Schema

Figure 1 Cohorts 1 to 8 Study Schema

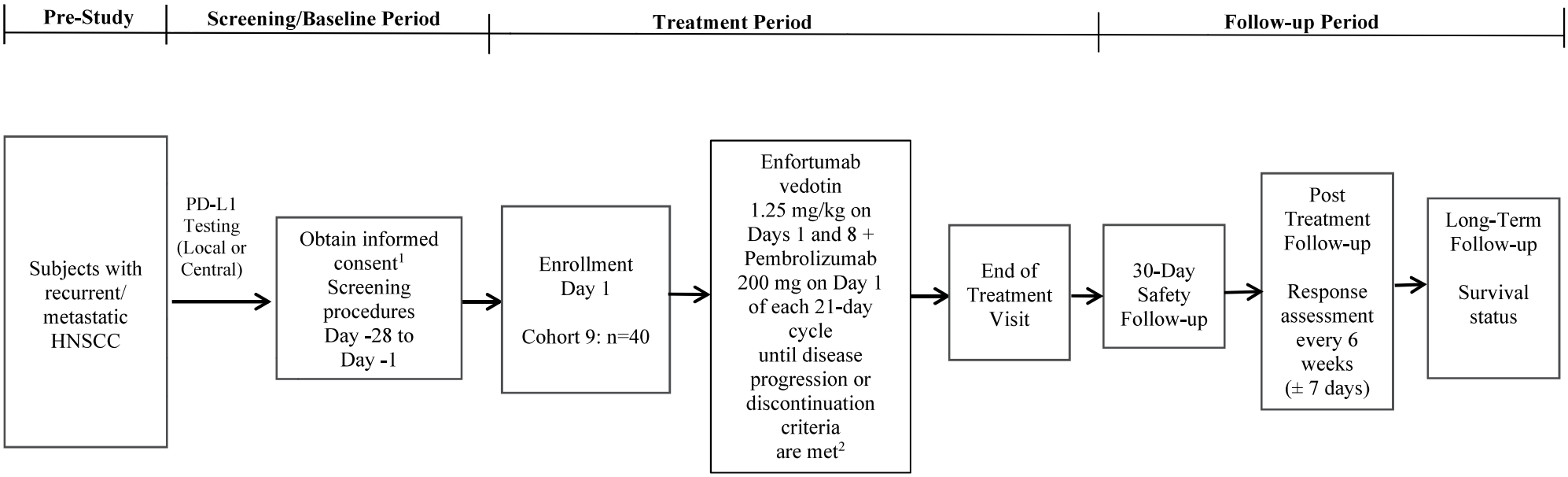


*Subjects initially enrolled in Cohort 6 will be reallocated to Cohort 7 or 8 based on tumor type/histology.

Disease assessment will be performed at screening/baseline and repeated every 8 weeks (56 days ± 7 days) from the first dose of study treatment throughout the study until the subject has radiologically-confirmed disease progression, initiates a new subsequent anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever comes first. A confirmatory imaging scan is required 4 weeks (28 days + 7-day window) after the first response.

After 1 year on study treatment, the frequency of response assessments will be reduced to every 12 weeks (84 days ± 7 days).

Figure 2 Cohort 9 Schema



CPS: combined positive score; HNSCC: head and neck squamous cell carcinoma; PD-L1: programmed death-ligand 1

1 Local PD-L1 test results may be used for eligibility and should be submitted to confirm positive PD-L1 status (CPS ≥1). If Local testing is unavailable then archival or fresh tissue must be submitted for central testing prior to enrollment; central PD-L1 testing results will be required prior to subject enrollment.

2 Disease assessment will be performed at screening/baseline. The first on-study disease assessment will be 9 weeks (± 7 days) from the first dose of study treatment and then every 6 weeks (± 7 days) throughout the study until the subject has radiologically-confirmed disease progression, initiates a new subsequent anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever comes first. A confirmatory imaging scan is required 4 weeks (28 days + 7-day window) after the first response. After 18 months on study treatment, the frequency of response assessments will be reduced to every 9 weeks (84 days ± 7 days).

1.3 Schedules of Assessments

Table 1 Schedule of Assessments – Cohorts 1 to 8

Period / Assessments	Screening/Baseline		Treatment								Follow-up		
			Cycle 1			Subsequent Every Cycle			Every 8 Weeks	EOT	30-day Safety Follow-up	Post Treatment Follow-up	Long-Term Follow-up
Cycle Day	-28 to -1	-7 to -1	1	8	15	1	8	15		Date of last dose [18]	30 days from last dose	Every 8 weeks	Every 12 weeks
Visit Window (Days)	0	0	0	± 3	± 3	± 3	± 3	± 3	± 7	+ 7	+ 7	± 7	± 7
General Study Procedures													
Informed Consent	X												
Confirmation of Eligibility per Inclusion/Exclusion Criteria	X		X										
Medical History/Disease History/Demographics	X												
Subject Enrollment			X										
Tumor Tissue Sample [1, 2]	X												
PGx Blood Sample (optional)		X											
Pregnancy Test [3]		X	X			X				X	pregnancy test monthly until 6 mo after last dose of study treatment		
Physical Examination [4]		X	X			X				X			
Weight		X	X			X				X			
Vital Signs		X	X	X	X	X	X	X		X			
ECOG Performance Status		X	X			X				X			
PRO/QOL [5]			X			X				X			
Survival [6]													X
Prior/Concomitant Medications [7]	Every visit												
AE Assessment [8]	Every visit												
Imaging													
Brain Scan [9]	X								X [9]			X [9]	
Bone Imaging [9]	X								X [9]			X [9]	
Image/Disease Assessment [10, 11]	X								X [11]			X [11]	

Period	Screening/Baseline		Treatment								Follow-up		
Assessments			**Cycle 1**			**Subsequent Every Cycle**			**Every 8 Weeks**	**EOT**	**30-day Safety Follow-up**	**Post Treatment Follow-up**	**Long-Term Follow-up**
Cycle Day	-28 to -1	-7 to -1	1	8	15	1	8	15		Date of last dose [18]	30 days from last dose	Every 8 weeks	Every 12 weeks
Visit Window (Days)	0	0	0	± 3	± 3	± 3	± 3	± 3	± 7	+ 7	+ 7	± 7	± 7
Clinical Laboratory Tests [12, 13]													
Hematology		X [12, 13]	X	X [13]	X	X				X			
Biochemistry		X [12, 13]	X	X [13]	X	X				X			
Hemoglobin A1c [14]		X [12, 13]								X			
Total cholesterol, HDL-C, LDL-C, Triglycerides		X [12, 13]											
Electrocardiograms													
12-lead ECG [15]		X								X			
Ophthalmology													
Complete Eye Exam [16]	X									X [16]			
Visit Window (Days)			0	+3	+3	+3	+3	+3					
Investigational Product Dispensing/Administration													
Enfortumab Vedotin [17]			X	X	X	X	X	X					

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PGx: pharmacogenomic; PRO: patient reported outcome; QOL: quality of life

1. Tumor tissue (from primary or metastatic site) for biomarker studies should be available for submission to the sponsor. If an archival tumor tissue sample is not available, the subject will have a biopsy to obtain tumor tissue prior to study treatment. Tumor tissue may be submitted as either a tissue block or freshly sectioned, unstained charged slides. A minimum of 10 and up to 20 slides are needed from each subject for the planned biomarker studies. If at least 10 slides cannot be sectioned from available block, please provide as many as possible and discuss with the sponsor. If multiple blocks will be used to produce slides, please contact the sponsor before cutting the blocks.
2. If any additional biopsy is performed as standard of care while on study treatment or during follow-up period, subject's tumor tissue samples are requested to be submitted as either a tissue block or freshly sectioned, unstained charged slides to the sponsor, if available.
3. For women of childbearing potential only. A serum pregnancy test will be performed at baseline. A urine or serum pregnancy test will then be repeated on day 1 of each cycle prior to study drug administration, at EOT and follow-up visits. After EOT, a monthly (±7 days) pregnancy test will be maintained until 6 months after the last dose of study treatment.
4. Full physical examination will be performed. Height measurement is only required at screening/baseline. Physical examination on cycle 1 day 1 is not necessary if it was performed within 7 days prior to the first day of dosing.
5. Quality of life questionnaires will be completed by the subject at the clinic visit prior to dosing and any other study assessments.

Footnotes continued on next page

6. After radiologically-confirmed disease progression or initiation of subsequent anticancer therapy, whichever occurs first, subjects will be contacted every 12 weeks in the long-term follow-up period for survival status until death, withdrawal of consent, lost to follow-up, or study closure, whichever occurs first. Sponsor may choose to discontinue the collection of survival status for any cohort.
7. Include all medications taken from the time of informed consent.
8. AEs will be collected from the time of informed consent through 30 days following the last dose of study treatment or until initiation of a new anticancer treatment, whichever occurs first.
9. Brain scan and bone imaging will be performed at screening/baseline. Repeat at response assessment time points if metastases were identified at screening/baseline, or if metastasis is known or suspected, or as clinically indicated throughout the study.
10. Imaging/disease assessment will be performed at screening/baseline and every 8 weeks (56 days ±7 days) from the first dose of study treatment throughout the study. Baseline imaging performed prior to informed consent as part of standard of care may be used as long as it is performed within 28 days prior to the first dose of study treatment. * Inclusion of neck anatomy, chest, abdomen, pelvis is required at all imaging visits for the head and neck cancer cohort, cervical/cervicothoracic junction and esophagus malignancy cancer types. Additional neck anatomy imaging should be performed as clinically indicated for all other cohorts. If neck imaging is obtained at a post-baseline timepoint, then it should be submitted at every timepoint thereafter. Copies of all imaging scans will also be sent to the independent review facility in a timely manner.
11. If disease response is assessed as complete response or partial response by investigator, a confirmatory imaging scan is required 4 weeks (28 days + 7-day window) after the first response. After 1 year on study treatment, the frequency of disease response assessments will be reduced to every 12 weeks (84 days ± 7 days).

    Subjects who discontinue study treatment for reasons other than consent withdrawal or radiologically-confirmed disease progression by RECIST Version 1.1 will continue to receive imaging scans every 8 weeks (56 days ± 7 days) until subject has radiologically-confirmed disease progression, initiates a new anticancer therapy, dies, withdraws consent, is lost to follow-up, or the study closes, whichever comes first. Tumor imaging may also be performed whenever disease progression is suspected.
12. See [Appendix 12.7 Laboratory Assessments]. Clinical laboratory tests will be performed locally prior to dosing. If tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on cycle 1 day 1.
13. Clinical laboratory tests at screening and on cycle 1 day 8 are to be performed after the subject has been fasting in order to ensure accurate interpretation of lab values such as glucose values. Fasting status will be recorded in source documents. Fasting is not necessary for laboratory tests performed at all other visits.
14. If HbA1c is elevated (≥ 6.5%), refer subject to appropriate provider during cycle 1 for glucose management.
15. Prior to performing 12-lead ECGs, subjects should rest in supine position (or semi-recumbent, if supine is not tolerated) for 10 minutes. ECGs will be read and assessed locally.
16. Repeated as clinically indicated throughout the study. Include but not limited to: visual acuity, slit lamp, tonometry examination, and dilated fundus examination. EOT slit lamp examinations are only required for subjects who experience ocular AEs during the study and must be performed ≥ 4 weeks from last dose.
17. At least 7 days must elapse between doses of enfortumab vedotin. Subjects should be observed during enfortumab vedotin administration and for at least 60 minutes following the infusion for the first 3 cycles.
18. The EOT visit should occur within 7 days of the last dose of enfortumab vedotin or when the decision is made by the investigator to discontinue the subject from treatment, or prior to the initiation of another anticancer therapy, whichever occurs earlier.

Table 2 Schedule of Assessments – Cohort 9

Period		Screening/Baseline		Treatment							Follow-up		
Assessments				**Cycles 1 and 2**			**Subsequent Every Cycle**		**Every 6 Weeks [11]**	**EOT**	**30-day Safety Follow-up**	**Post Treatment Follow-up**	**Long-Term Follow-up**
Cycle Day		-28 to -1	-7 to -1	1	8	15	1	8		Date of last dose [21]	30 days from last dose	Every 9 weeks [12]	Every 12 weeks
Visit Window (Days)		0	0	0	± 3	± 3	± 3	-1 to + 4	± 7	+ 7	+ 7	± 7	± 7
General Study Procedures													
Informed Consent		X											
Tumor Tissue Sample [1,2]		X											
PD-L1 Test Result [3]		X											
Confirmation of Eligibility per Inclusion/Exclusion Criteria		X		X									
Medical History/Disease History/Demographics		X											
Subject Enrollment				X									
PGx Blood Sample (optional)			X										
Pregnancy Test [4]			X	X			X			X	Pregnancy test monthly until 6 mo after last dose of study treatment		
Physical Examination [5]			X	X			X			X		X	
Weight			X	X			X			X			
Vital Signs			X	X	X		X	X		X			
ECOG Performance Status			X	X			X			X		X	
PRO/QOL [6]				X	X	X	X	X		X	X		
Survival [7]													X
Prior/Concomitant Medications [8]		Every visit											
AE Assessment [9]		Every visit											
Imaging													
Image/Disease Assessment [10, 11]		X							X [10, 11]			X [11]	

Period		Screening/Baseline		Treatment							Follow-up		
Assessments				**Cycles 1 and 2**			**Subsequent Every Cycle**		**Every 6 Weeks [11]**	**EOT**	**30-day Safety Follow-up**	**Post Treatment Follow-up**	**Long-Term Follow-up**
Cycle Day		-28 to -1	-7 to -1	1	8	15	1	8		Date of last dose [21]	30 days from last dose	Every 9 weeks [12]	Every 12 weeks
Visit Window (Days)		0	0	0	± 3	± 3	± 3	-1 to + 4	± 7	+ 7	+ 7	± 7	± 7
Clinical Laboratory Tests [13,14]													
Hematology			X [13,14]	X [13]	X [14]	X [15]	X	X		X			
Biochemistry			X [13,14]	X [13]	X [14]	X [15]	X	X		X			
Hemoglobin A1c			X [13,14]							X			
Total cholesterol, HDL-C, LDL-C, Triglycerides			X [13,14]										
Thyroid Function Tests			X	X			X [16]						
Coagulation			X										
Electrocardiograms													
12-lead ECG [17]			X							X			
Ophthalmology													
Complete Eye Exam [18]		X								X [18]			
Investigational Product Dispensing/Administration													
Enfortumab Vedotin [19]				X	X		X	X					
Pembrolizumab [20]				X			X						

AE: adverse event; CPS: combined positive score; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; HDL-C: high-density lipoprotein cholesterol; iRECIST: modified RECIST v1.1 for immune-based therapeutics; LDL-C: low-density lipoprotein cholesterol; PD-L1: programmed death-ligand 1; PGx: pharmacogenomic; PRO: patient reported outcome; QOL: quality of life

1. Tumor tissue (from primary or metastatic site) for PD-L1 testing and biomarker studies should be available for submission to the sponsor. If an archival tumor tissue sample is not available for screening/baseline, the subject will have a biopsy to obtain tumor tissue prior to study treatment. Tumor tissue may be submitted as either a tissue block or freshly sectioned, unstained charged slides. A minimum of 10 and up to 20 slides are needed from each subject for the planned biomarker studies. If at least 10 slides cannot be sectioned from available block, please provide as many as possible and discuss with the sponsor. If multiple blocks will be used to produce slides, please contact the sponsor before cutting the blocks.
2. If any additional biopsy is performed as standard of care while on study treatment or during follow-up period, subject's tumor tissue samples are requested to be submitted as either a tissue block or freshly sectioned, unstained charged slides to the sponsor, if available.

Footnotes continued on next page

3. Local PD-L1 test results may be used for eligibility and should be submitted to confirm positive PD-L1 status (CPS ≥1). If Local testing is unavailable then archival or fresh tissue must be submitted for central testing prior to enrollment; central PD-L1 testing results will be required prior to subject enrollment.
4. For women of childbearing potential only. A serum pregnancy test will be performed at baseline. A urine or serum pregnancy test will then be repeated on day 1 of each cycle prior to study drug administration, at EOT and follow-up visits. After EOT, a monthly (±7 days) pregnancy test will be maintained until 6 months after the last dose of study treatment.
5. Full physical examination will be performed. Height measurement is only required at screening/baseline. Physical examination on cycle 1 day 1 is not necessary if it was performed within 7 days prior to the first day of dosing.
6. Quality of life questionnaires will be completed by the subject at the clinic visit prior to dosing and any other study assessments.
7. After radiologically-confirmed disease progression or initiation of subsequent anticancer therapy, whichever occurs first, subjects will be contacted every 12 weeks in the long-term follow-up period for survival status until death, withdrawal of consent, lost to follow-up, or study closure, whichever occurs first. Sponsor may choose to discontinue the collection of survival status for any cohort.
8. Include all medications taken from the time of informed consent.
9. AEs will be collected from the time of informed consent through 30 days following the last dose of study treatment. SAEs related to pembrolizumab will be collected from Day 1 through 90 days after the last study treatment, or 30 days following cessation of study treatment if the subject initiates a new anticancer therapy.
10. The first on-study disease assessment will be performed 9 weeks (63 days ±7 days) from the first dose of study treatment and then every 6 weeks (42 days ±7 days) throughout the study and assessed by the investigator per RECIST v1.1. Imaging should include the head, neck, chest and abdomen at the specified timepoints. A CT from the vertex of the head to the thoracic inlet or a brain CT is strongly preferred. Imaging of the pelvis is optional. After 18 months on study treatment, the frequency of disease response assessments will be reduced to every 9 weeks (63 days ± 7 days). Baseline imaging performed prior to informed consent as part of standard of care may be used as long as it is performed within 28 days prior to the first dose of study treatment. Tumor imaging should also be performed whenever disease progression is suspected. Objective responses will be confirmed per RECIST v1.1 with repeat scans at least 4 weeks (28 days +7 days) after first documentation of response.
11. iRECIST should be assessed in parallel with all RECIST v1.1 assessments at every timepoint. Subjects with unconfirmed progressive disease (iUPD) may continue on study treatment until iCPD per iRECIST guidelines [Seymour et al, 2017] as assessed by the investigator. Confirmatory scans will be performed at the next scheduled disease assessment (6 weeks ± 7 days).
12. Subjects who discontinue treatment for reasons other than radiologically-confirmed disease progression per iRECIST will have physical exams, ECOG and disease assessments every 6 weeks (± 1 week) up to 18 months after first dose, then every 9 weeks (± 1 week) until the subject has radiologically confirmed disease progression per iRECIST as determined by the investigator, initiates a subsequent anticancer therapy, dies, withdraws consent, or the study closes. During study treatment, palliative radiotherapy on a nontarget lesion that is not progressing will not be considered a subsequent anticancer therapy; however, radiotherapy on any target lesion will be a subsequent anticancer therapy.
13. See [Appendix 12.7 Laboratory Assessments]. Clinical laboratory tests will be performed locally prior to dosing. If tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on cycle 1 day 1.
14. Clinical laboratory tests at screening and on cycle 1 day 8 are to be performed after the subject has been fasting in order to ensure accurate interpretation of lab values such as glucose values. Fasting status will be recorded in source documents. Fasting is not necessary for laboratory tests performed at all other visits. If HbA1c is elevated (≥ 6.5%), refer subject to appropriate provider during cycle 1 for glucose management.
15. Day 15 clinical laboratory tests only required for cycles 1 and 2, unless clinically indicated.

Footnotes continued on next page

16. Thyroid function tests (Triiodothyronine [T3] or Free Triiodothyronine [FT3], Free thyroxine [FT4] and Thyroid stimulating hormone [TSH] required at cycle 1, cycle 2 and every odd cycle during the treatment period (i.e., cycles 3, 5, 7 etc.)
17. Prior to performing 12-lead ECGs, subjects should rest in supine position (or semi-recumbent, if supine is not tolerated) for 10 minutes. ECGs will be read and assessed locally.
18. Repeated as clinically indicated throughout the study. Include but not limited to: visual acuity, slit lamp, tonometry examination, and dilated fundus examination. EOT slit lamp examinations are only required for subjects who experience ocular AEs during the study and must be performed ≥ 4 weeks from last dose.
19. At least 7 days must elapse between doses of enfortumab vedotin. Subjects should be observed during enfortumab vedotin administration and for at least 60 minutes following the infusion for the first 3 cycles.
20. Pembrolizumab should be administered approximately 30 minutes after completion of enfortumab vedotin administration.
21. The EOT visit should occur within 7 days of the last dose of enfortumab vedotin or when the decision is made by the investigator to discontinue the subject from treatment, or prior to the initiation of another anticancer therapy, whichever occurs earlier.

1.3.1 Sample Collection Schedule

Table 3 Pharmacokinetic, Antitherapeutic Antibodies, and Biomarker Blood Sample Collection Time Points – Cohorts 1 to 8

					Blood				
							Biomarkers		
	Study Day	Time	Window[1]	Relative Time	Pharmacokinetics	ATA	Soluble Circulating Factors	cf DNA	Immuno-phenotyping
Cycle 1	Day 1	Predose	Within 24 hrs	START of infusion	X	X	X	X	X
		End of infusion	Within 15 min	END of infusion	X				
	Day 8	Predose	Within 24 hrs	START of infusion	X		X	X	X
	Day 15	Predose	Within 24 hrs	START of infusion	X		X	X	X
		End of infusion	Within 15 min	END of infusion	X				
Cycle 2	Day 1	Predose	Within 24 hrs	START of infusion	X	X	X	X	X
Subsequent Dosing Cycles	Day 1	Predose	Within 24 hrs	START of infusion	X[2]	X[2]	X[3]	X[3]	X[3]
End of Treatment (date of last dose + 7-day window)					X	X	X	X	X
Follow-up (30 days from last dose + 7-day window)					X	X	X	X	

ATA: antitherapeutic antibodies; cfDNA: circulating free deoxyribonucleic acid

1. Allowed window for blood samples collected at predose is within 24 hours before the start of infusion. The window for samples collected at end of infusion is within 15 minutes after the end of infusion
2. Pharmacokinetics and ATA: predose of cycles 4, 7 and 12.
3. Soluble circulating factors, cfDNA and immuno-phenotyping: predose cycles 3 and 4 only.

Table 4 Pharmacokinetic, Antitherapeutic Antibodies, and Biomarker Blood Sample Collection Time Points – Cohort 9

	Study Day	Time	Window[1]	Relative Time	Blood				
							Biomarkers		
					EV PK	EV ATA	Soluble Circulating Factors	cf DNA	Immuno-phenotyping
Cycle 1	Day 1	Predose	Within 24 hrs	START of infusion	X	X	X	X	X
		End of infusion	Within 15 min	END of infusion	X				
	Day 8	Predose	Within 24 hrs	START of infusion	X		X	X	X
Cycle 2	Day 1	Predose	Within 24 hrs	START of infusion	X	X	X	X	X
Subsequent Dosing Cycles	Day 1	Predose	Within 24 hrs	START of infusion	X[2]	X[2]	X[3]	X[3]	X[3]
End of Treatment (date of last dose + 7-day window)					X	X	X	X	X
Follow-up (30 days from last dose + 7-day window)					X	X	X	X	

ATA: antitherapeutic antibodies; cfDNA: circulating free deoxyribonucleic acid; EV: enfortumab vedotin; PK: pharmacokinetics

1. Allowed window for blood samples collected at predose is within 24 hours before the start of infusion. The window for samples collected at end of infusion is within 15 minutes after the end of infusion
2. PK and ATA: predose of cycles 4, 7 and 12.
3. Soluble circulating factors, cfDNA and immuno-phenotyping: predose cycles 3 and 4 only.

2 INTRODUCTION

Cancer is the leading cause of death in the US for people 35 to 65 years of age and it is the second leading cause of death worldwide. It was estimated in 2021 that there would be approximately 1.9 million new cancer cases and approximately 608000 deaths from cancer in the US [National Cancer Institute, 2021a]. Cancer accounted for nearly 10 million deaths worldwide in 2020 [World Health Organization, 2021a]. Most deaths now occur in patients with metastatic cancers. In fact, in the last 20 years, advances in treatment, including surgery, radiotherapy and adjuvant chemotherapy cured most patients with localized cancer. Patients whose cancer presented or recurred as metastatic disease obtained only modest benefit from conventional therapies in terms of overall survival (OS) and were rarely cured.

New therapeutic strategies for metastatic cancers include targeting molecular pathways important for cancer cell survival and novel cytotoxic compounds. The benefit of these novel drugs is reflected in prolonged survival; however, the outcome for most patients with distant metastases is still poor and novel therapies are needed.

Enfortumab vedotin targets the cell adhesion protein Nectin-4. Nectin-4 is a type I transmembrane protein and member of a family of related immunoglobulin-like adhesion molecules implicated in cell-to-cell adhesion. Nectin-facilitated adhesion supports several biological processes, such as immune modulation, host-pathogen interaction, and immune evasion [Sakisaka et al, 2007]. Nectin-4 is highly expressed in cancer cells, particularly in urothelial cancers, breast cancer, non-small cell lung cancer (NSCLC), and other epithelial tumors, with moderate expression observed in normal human skin [Deng et al, 2019; Zhang et al, 2018a; Takano et al, 2009; Fabre-Lafay et al, 2007]. In several cancers, including breast cancer, lung cancer, gastric cancer and esophageal cancer, Nectin-4 expression is associated with cancer progression and poor prognosis. Although the exact role of Nectin-4 expression in cancer is not yet known, the high expression in certain cancers also creates an ideal treatment target for these malignancies. Enfortumab vedotin (previously known as ASG-22CE) is a novel, fully humanized, monoclonal antibody-drug conjugate (ADC) that delivers a microtubule-disrupting agent, monomethyl auristatin E (MMAE), to cells expressing Nectin-4 [Sakisaka et al, 2007]. Enfortumab vedotin selectively binds to Nectin-4-expressing cells, initiating internalization of the ADC-Nectin-4 complex and proteolytic cleavage of the conjugated MMAE, disrupting microtubule networks and resulting in apoptotic cell death.

Targeting tumors with enfortumab vedotin, which targets Nectin-4, could provide a novel approach to the treatment of certain cancers such as urothelial, lung, breast, head and neck, gastric, and esophageal cancers [Challita-Eid et al, 2016; Zhang et al, 2018a]. They are representative of tumors with moderate to high Nectin-4 expression, and for which there is preclinical or clinical evidence of sensitivity to enfortumab vedotin, or supportive evidence based on published literature, in addition to known sensitivity to microtubule-disrupting agents [Challita-Eid et al, 2016; Deng et al, 2019; Zhang et al, 2018b].

2.1 Background

2.1.1 Breast Cancer

Globally, there were approximately 2.3 million newly diagnosed female breast cancer cases in 2020, accounting for almost 1 in 4 cancer cases among women [World Health Organization, 2021b]. The disease is the most frequently diagnosed cancer in the vast majority of countries and is also the leading cause of cancer-related death in women. Following metastatic diagnosis, prognosis is poor with a with a 5-year survival rate of approximately 28%.

The selection of appropriate therapy for metastatic breast cancer is complex because of the many treatment options and biologic heterogeneity of the disease. The potential treatment options are influenced by estrogen and progesterone receptors and by human epidermal growth factor receptor 2 (HER2) status of the tumor. Treatment options for subjects presenting with metastatic breast cancer may also be influenced by what adjuvant therapy was used, how soon after adjuvant therapy the subject relapses, and by sites of metastasis.

2.1.1.1 Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative Breast Cancer

Hormone receptor positive (HR+)/HER2-negative breast cancer is the most common breast cancer subtype (> 70%), occurring predominantly in postmenopausal women. The initial treatment for women with metastatic disease consists primarily of endocrine therapy. This is usually administered alone, in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor, or as dual endocrine blockade. For women who are endocrine refractory or women who have symptomatic visceral disease, systemic chemotherapy is recommended.

Several cytotoxic chemotherapy agents have shown activity in metastatic breast cancer, including anthracyclines, taxanes, gemcitabine, capecitabine, vinorelbine, eribulin and ixabepilone. The response rates with these agents vary depending on the type of prior therapy, as well as the breast cancer subtype. In general, anthracycline-based combination therapy and taxanes such as paclitaxel and docetaxel are thought to be the most active [Piccart, 2008]. Given the wide use of anthracyclines in the adjuvant setting and the increased risk of cardiotoxicity, the use of anthracyclines in the metastatic setting is limited. Taxanes are the most commonly used agent for patients with locally advanced or metastatic disease, particularly in the front-line setting [Greene & Hennessy, 2015]. About 70% of Stage II–III patients receive neoadjuvant anthracycline, cyclophosphamide with a taxane, which limits use of these agents in the metastatic setting [Kantar, 2019]. Sequential single agent therapies are recommended over combinations due to lower toxicities and limited survival benefit. Responses to commonly used single agent chemotherapy patients with HR+/HER2-negative breast cancer are primarily limited to subgroup analysis, these have ranged between 11% to 36% [Robson et al, 2017; Kaufman et al, 2015; Cortes et al, 2011]. In general, responses tended to be lower in pretreated patients with reported ranges between 10% to 13% [Perez et al, 2007; Jones et al, 1995].

2.1.1.2 Triple Negative Breast Cancer

Triple negative breast cancer (TNBC) is defined by the absence of immunostaining for estrogen receptor (ER), progesterone receptor (PR) and HER2. Overall, approximately 15% to 20% of breast cancers are classified as TNBC. TNBC is associated with aggressive tumor biology, visceral metastasis, and a poor prognosis [Plasilova et al, 2016].

Taxane-based regimens are considered a standard of care in first-line therapy for patients with metastatic breast cancer, including TNBC. More recently the FDA granted accelerated approval for atezolizumab in combination with nab-paclitaxel for the treatment of patients with unresectable locally advanced or metastatic TNBC whose tumors express programmed death-ligand 1 (PD-L1). The approval was based on a median progression-free survival (PFS) of 7.5 months for atezolizumab plus nab-paclitaxel versus 5.0 months in the placebo plus nab-paclitaxel arm; objective response rate (ORR) of 56% versus 46%) [Schmid et al, 2019]. The FDA also granted accelerated approval to pembrolizumab in combination with chemotherapy for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (combined positive score [CPS] $\geq$ 10). In patients with CPS $\geq$10, the addition of pembrolizumab to chemotherapy improved median PFS by approximately 2 months (9.7 versus 5.6 months; HR 0.65, 95% CI 0.49-0.86) [Cortes et al, 2020].

Options are limited for second- or further-line treatment, and options for chemotherapy are the same as those for other subtypes. In 2021, the FDA granted approval to sacituzumab govitecan for patients with unresectable locally advanced or metastatic TNBC who have received 2 or more prior systemic therapies, at least one of them for metastatic disease. Single agent pembrolizumab is also approved by the FDA for patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, or TMB-H tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. However, pembrolizumab is only an option for patients who have previously not been treated with a PD-1/ PD-L1 inhibitor [Keytruda prescribing information, 2021]. Single agent cytotoxic chemotherapeutic agents are generally preferred over combination chemotherapy due to the lack of survival benefit and increased toxicity except in the setting of aggressive disease and visceral involvement [Cardoso et al, 2017; National Comprehensive Cancer Network, 2019]. Standard chemotherapy among pretreated patients is associated with low response rates (10% to 15%) and short progression-free survival (2 to 3 months) [Hurvitz & Mead, 2016].

2.1.2 Non-small Cell Lung Cancer

Lung cancer (both small cell and non-small cell) is the leading cause of cancer deaths in the US [American Cancer Society, 2021a]. Most patients diagnosed with lung cancer are 65 years of age or older and, the average age at the time of diagnosis is approximately 70 years of age.

Non-small cell lung cancer accounts for approximately 84% of all lung cancers and can be subclassified as squamous (approximately 30% of NSCLC cases) and non-squamous (approximately 70% of NSCLC cases) histological types [American Cancer Society, 2021a].

2.1.2.1 Squamous Non-small Cell Lung Cancer

Squamous NSCLC is a distinct histological subtype of NSCLC that is challenging to treat as a result of specific patient and disease characteristics, which include older age, advanced disease at diagnosis, comorbid disease, and the central location of tumors [Socinski et al, 2018]. These characteristics have a bearing on treatment outcomes in advanced squamous NSCLC, resulting in a median survival rate of approximately 30% shorter than for patients with other NSCLC subtypes.

Once immunotherapy has been utilized, there are limited treatment options, especially for later line treatment of advanced squamous NSCLC, with a resultant impact on survival outcomes [National Comprehensive Cancer Network, 2021b; Novello et al, 2016; Masters et al, 2015]. Given the recent approvals of targeted therapies and immunotherapies for advanced NSCLC and continuation towards personalization of lung cancer treatment, there is also a need to evaluate the effectiveness of these new treatments for advanced squamous NSCLC. In addition, as targeted and immunotherapies shift earlier in the treatment paradigm, there will be limited options for later line treatment.

2.1.2.2 Non-squamous Non-small Cell Lung Cancer

Non-squamous NSCLC is a heterogenous disease with multiple treatment options dependent upon staging, presence of metastasis, and patient factors, including presence of comorbidities among other considerations. As such, current treatment options include surgical resection, chemotherapy, radiation, immunotherapy, and targeted therapy. Currently, the first-line therapy for patients with advanced or metastatic non-squamous NSCLC without targetable genetic aberrations is platinum-doublet chemotherapy plus pembrolizumab followed by maintenance therapy with at least one of the agents used in first line, either as continuation maintenance or as switch maintenance. Nivolumab with ipilimumab can also be used with platinum doublet chemotherapy. For patients with contraindications to PD-1/ PD-L1 inhibitors, bevacizumab is often used as an alternative regimen. Second line therapy for patients who have received immunotherapy in first line consists of docetaxel with or without ramucirumab, or single agent pemetrexed or gemcitabine [National Comprehensive Cancer Network, 2019]. With the exception of bevacizumab, and despite extensive study of multiple targeted and cytotoxic agents, the addition of a third agent to platinum-doublet chemotherapy has not been shown to improve progression-free or OS over platinum-doublet chemotherapy alone in randomized studies [Reck et al, 2010; Sandler et al, 2006].

2.1.3 Head and Neck Cancer

Head and neck cancer is a group of cancers that starts in the mouth, nose, throat, pharynx, larynx, sinuses, or salivary glands [National Cancer Institute, 2017]. Squamous cell carcinoma is the most frequent histological subtype of head and neck cancers, beside other rare histological types. Squamous cell carcinoma arises from the mucosal epithelium in the

oral cavity, pharynx and larynx and are known collectively as head and neck squamous cell carcinoma (HNSCC).

Worldwide, HNSCC is the 7th most common cancer (excluding nonmelanoma skin cancer), and accounts for approximately 900 000 new cases and over 400 000 deaths annually. The incidence of HNSCC continues to rise and is anticipated to increase by 30% (that is, 1.08 million new cases annually) by 2030 [Global Cancer Observatory, 2021]. South Asia has the highest head and neck cancer incidence rate, followed by Europe, North America, and Australasia [Aupérin, 2020]. In the United States, head and neck cancer accounts for 3% of malignancies, with approximately 66 000 patients developing head and neck cancer annually and 14 600 dying from the disease [Siegel, 2021]. Men are at higher risk of developing HNSCC with a ratio of male to female ranging from 2:1 to 4:1 [Johnson et al, 2020]. The median age of diagnosis for non-HPV (human papilloma virus) HNSCC is 66 years, whereas the median age of diagnosis for HPV-associated oropharyngeal cancer is 55 years [Windon et al, 2018].

The most common and consistent risk factors for HNSCC is tobacco and alcohol, which have multiplicative (synergistic) effect increasing the risk of developing HNSCC by 35-fold in heavy users of both substances [Blot, 1988]. A more recently identified risk factor for HNSCC is exposure to high-risk types of HPV, with an increasing incidence in HPV-associated oropharyngeal cancer (OPC).

The survival for HNSCC has only modestly improved over the past three decades, because patients often develop locoregional recurrences, distant metastases and second primary tumors. About 50% of patients with locally advanced HNSCC at diagnosis, develop recurrent and/or metastatic HNSCC, despite advances in multimodality therapy (combination of surgery, radiation therapy, chemotherapy, and targeted therapy [Leeman et al, 2017]. Patients with recurrent and/or metastatic HNSCC have a very poor prognosis with a median overall survival (OS) of less than one year [Argiris et al, 2017].

Immunotherapy with immune check point inhibitors, has recently made a breakthrough in medical oncology in many different tumor types, including recurrent/metastatic HNSCC. Nivolumab and Pembrolizumab were the two PD-1 monoclonal antibody inhibitors approved in 2016 by the FDA in the second-line setting in recurrent/metastatic HNSCC who had progression of disease on platinum, and thus established a new standard of care (SOC) in the second line setting. They were later approved in Europe for the same indication and Nivolumab was approved in Japan [Ferris et al, 2019]. At the present time, no recommendations exist based on clinical trial data on how to treat recurrent/metastatic HNSCC patients after exposure to first-line immunotherapy +/− chemotherapy.

There has also been a recent paradigm change (2019 in US, Europe, Japan) in first line therapy of recurrent/metastatic HNSCC with Pembrolizumab +/- chemotherapy (platinum plus 5FU) based on the results of KEYNOTE-048 trial, which is the first trial since the publication of the EXTREME study (2008) to show OS improvement in the first line setting [Vermorken et al, 2008; Burtness et al, 2019]. In the second interim analysis of the KEYNOTE-048 study, in the PD-L1 CPS $\geq$ 1 population, the median overall survival was

12.3 months (95% CI 10.8, 14.9) for the pembrolizumab monotherapy group versus 10.3 months (95% CI 9.0, 11.5) in the cetuximab plus chemotherapy group; HR was 0.78 (95% CI 0.64, 0.96, p = 0.0086). The benefit of pembrolizumab monotherapy compared with cetuximab plus chemotherapy in the CPS $\geq$ 1 population was maintained at the final analysis (median OS 13.6 months for pembrolizumab monotherapy vs. 10.4 months for cetuximab plus chemotherapy; HR 0.65 (95% CI 0.53, 0.80)

In the NCCN, ESMO and ESMO Pan-Asian guidelines, single agent pembrolizumab is considered a preferred regimen for patients with first line unresectable recurrent/metastatic HNSCC with CPS $\geq$ 1 (NCCN Category 1, ESMO MCBS 4). Pembrolizumab plus chemotherapy is also a NCCN Category 1, ESMO MCBS 4 recommendation for first line unresectable recurrent/metastatic HNSCC patients regardless of PD-L1 status [National Comprehensive Cancer Network, 2023; Keam, 2021; Machiels, 2020]. The choice of pembrolizumab monotherapy or chemotherapy plus pembrolizumab is based on CPS, tumor burden and symptoms [Keam, 2021]. Despite these recent advancements in the treatment of recurrent/metastatic HNSCC in the first and second-line setting, there is still an unmet medical need for new therapies both in first line patients and following progression of disease on platinum and PD-1 inhibitors.

2.1.4 Gastric, Gastroesophageal Junction and Esophageal Cancer

Gastroesophageal cancers which include esophageal squamous cell carcinoma (ESCC), esophageal adenocarcinoma, gastroesophageal junction (GEJ) adenocarcinoma and gastric adenocarcinoma accounted for > 1.6 million new cases and more than 1 million deaths worldwide in 2020 [Global Cancer Observatory, 2021]. Gastroesophageal adenocarcinoma (GEAC) and squamous cell carcinoma have distinct epidemiological, genetic and molecular characteristics [Siewert, 2007]. The majority of gastric and GEJ cancers are adenocarcinomas, whereas the majority of esophageal cancers are of squamous histology [National Comprehensive Cancer Network, 2021d]. Gastroesophageal adenocarcinomas are generally more prevalent in North America and Western Europe, while ESCC is the most common histology in Eastern Europe and Asia. At present, gastroesophageal adenocarcinomas including adenocarcinomas of the GEJ and proximal stomach are increasing in incidence in Western countries, whereas the incidence of adenocarcinomas of the distal stomach are decreasing [National Comprehensive Cancer Network, 2021c]. The incidence of ESCC, which is often associated with alcohol and/or tobacco use, is declining in the West due to reduced alcohol and tobacco use, and currently accounts for < 30% of all esophageal cancers in the US and Western Europe.

In first line, the systemic therapy regimens used to treat advanced gastric, GEJ, and esophageal cancers are very similar. The preferred chemotherapeutic backbone regimen includes a fluoropyrimidine combined with a platinum-based agent [National Comprehensive Cancer Network, 2021c,d]. Biomarker assessment has become critically important for selection of 1L systemic therapy and it is recommended that patients should have their tumors assayed for HER2, PD-L1, mismatch repair deficiency, and microsatellite instability. For patients who have tumors that overexpress HER2, trastuzumab should be added

[Yoon, 2021a] to first line cytotoxic agents. First-line therapy with an immune checkpoint inhibitor in combination with cytotoxic chemotherapy has been shown to improve outcomes over cytotoxic chemotherapy alone for both gastroesophageal adenocarcinoma and squamous cell carcinomas. In adenocarcinomas, immune checkpoint inhibitors have shown benefit when added to cytotoxic chemotherapy in patients with tumoral overexpression of PD-L1 and a CPS of 5 or more, as well as in patients with tumors deficient in mismatch repair (dMMR). Recent evidence suggests that PD-L1 overexpression may be a predictor of efficacy in squamous cell carcinoma as well.

Following failure of the first-line regimen, the currently available standard of care differs for GEAC (which has a variety of recommended 2L+ options) versus squamous cell carcinoma (where available treatment options are more limited). Second-line therapy is guided on case-by-case factors including performance status, comorbidity, patient preference, symptom burden and quality of life. The tumor histologic type, molecular analysis and the nature of the first-line regimen are also key considerations for subsequent treatment. For patients with GEAC, several options may be utilized after first-line progression. For HER2-positive GEAC, potential benefit has been shown for the antibody-drug conjugate fam-trastuzumab deruxtecan after progression on first-line trastuzumab. Patients with GEAC who have PD-L1 overexpression, dMMR/MSI-H or high TMB may benefit from treatment with pembrolizumab, if an immune checkpoint inhibitor was not administered for first-line therapy. Patients with HER2-negative adenocarcinoma who have disease progression on or after prior treatment with fluroropyrimidine- or platinum-containing chemotherapy, and who are not eligible for or had disease progression with PD-1 targeted immunotherapy, may be treated with ramucirumab monotherapy or with a taxane. Trifluridine/tipiracil is a common third-line option for patients with adenocarcinoma that is PD-L1 negative and has proficient mismatch repair, and is utilized as a fourth-line option for patients with PD-L1-positive/dMMR adenocarcinoma [Yoon, 2021b].

Patients with ESCC have more limited options after failure of the first-line regimen. Patients eligible for immunotherapy, regardless of PD-L1 or MMR or TMB status, may be treated with nivolumab monotherapy (or camrelizumab where available) if PD-1 targeted immunotherapy was not utilized in the first line. Rechallenge with immunotherapy is generally not pursued, unless in the context of a clinical trial or if the immunotherapy was discontinued due to a specific toxicity that has since resolved [Yoon, 2021b]. For patients who are not eligible for immunotherapy, a combination cytotoxic chemotherapy regimen not used in the first line is the recommended standard of care for patients who maintain an excellent performance status, favorable comorbidity and who are amenable to intensive treatment.

The differences in the pathophysiology and treatment algorithms between GEAC and ESCC support the rationale for their separation into distinct cohorts in EV-202.

2.2 Enfortumab Vedotin

ADCs, which consist of novel, highly active cytotoxics linked to monoclonal antibodies (mAbs) against cancer-specific targets, are potentially safer and more effective than

conventional chemotherapy. The rationale underlying therapy with ADCs is to target drug delivery. The antibody treatment typically targets molecules expressed or prevalent on the surface of cancer cells; therefore, delivering maximum anticancer effects with minimal toxicity.

Enfortumab vedotin is an ADC comprised of a fully human immunoglobulin G1 kappa ($IgG1_K$) antibody conjugated to the microtubule-disrupting agent (MMAE) via a protease-cleavable linker [Challita-Eid et al, 2016]. Enfortumab vedotin is thought to induce antitumor activity by binding to Nectin-4 protein on the cell surface leading to internalization of the ADC-Nectin-4 complex, which then traffics to the lysosomal compartment where MMAE is released via proteolytic cleavage of the linker. Intracellular release of MMAE subsequently disrupts tubulin polymerization resulting in G2/M phase cell cycle arrest and apoptotic cell death [Francisco et al, 2003].

Nectin-4 is a 66 kDa type I transmembrane protein that belongs to the Nectin family of adhesion molecules. It is composed of an extracellular domain (ECD) containing 3 Ig-like subdomains, a transmembrane helix, and an intracellular region [Takai et al, 2008]. Nectins are thought to mediate Ca^{2+}-independent cell-cell adhesion via both homophilic and heterophilic trans interactions at adherens junctions where they can recruit cadherins and modulate cytoskeletal rearrangements [Rikitake & Takai, 2008]. Sequence identity of Nectin-4 to other Nectin family members is low and ranges between 25% to 30% in the ECD [Reymond et al, 2001].

2.2.1 Nonclinical and Clinical Data

2.2.1.1 Pharmacology

Immunohistochemical studies demonstrated expression of Nectin-4 and Nectin-4 mRNA on a variety of tumor types including, but not limited to, bladder, breast, pancreatic and lung. In vitro pharmacology studies demonstrated specific, high affinity binding of AGS-22M6E and AGS-22M6 (unconjugated antibody) to Nectin-4 expressed on human cancer cells [Challita-Eid et al, 2016].

AGS-22M6E bound human Nectin-4 antigen with high affinity and cross-reacted with similar affinity to cynomolgus monkey, rat and, with lower affinity, mouse orthologs of Nectin-4. In addition, enfortumab vedotin bound human Nectin-4 with comparable affinity to AGS 22M6E. AGS-22M6E did not cross-react with other Nectin family members, such as Nectin-1, -2 or -3.

In vitro, AGS-22M6E was internalized by cells that endogenously express Nectin-4, as well as by cell lines engineered to express Nectin-4 on the cell surface. Internalization reached maximum levels by 4 hours and decreased thereafter. The released payload, MMAE, was shown to be specifically delivered following Nectin-4 antigen engagement. MMAE was delivered to the intracellular compartment of Nectin-4-transfected cells by enfortumab vedotin, while the parent cell line that did not express Nectin-4 had undetectable levels of MMAE, indicating that enfortumab vedotin delivery is Nectin-4 dependent.

Nectin-1 has been shown to bind to Nectin-4; however, Nectin-1 inhibition of enfortumab vedotin induced cytotoxicity could not be demonstrated. Enfortumab vedotin produced direct cell killing of Nectin-4-positive tumor cells and indirect bystander effect killing of surrounding Nectin-4-negative tumor cells in a concentration-dependent manner.

Pharmacodynamic bridging studies of AGS-22M6E and enfortumab vedotin confirmed comparable binding affinity, cytotoxicity and in vivo efficacy between the 2 ADCs.

In vivo and in vitro safety pharmacology parameters showed no effects in the CNS, respiratory and cardiovascular systems indicating an acceptable safety profile for these organ systems [Investigator Brochure].

Refer to the current Investigator's Brochure for detailed nonclinical pharmacology data.

2.2.1.2 Toxicology

The toxicities observed following intravenous administration of enfortumab vedotin in animals were consistent with target-mediated uptake of enfortumab vedotin as well as some target-independent effects of MMAE. Target-mediated skin toxicity correlated with Nectin-4 expression. Bone marrow hypocellularity was the primary target-independent toxicity observed, and was observed with both the ADC and MMAE. The toxicological target organs of skin, bone marrow, eye (corneal epithelium) and intestine correlated with clinically observed toxicities and were reversible following cessation of treatment. No toxicities were observed with the unconjugated antibody, suggesting no impact from antigen binding alone. There were no indications of altered glucose homeostasis in the nonclinical toxicology program.

Intravesical administration of enfortumab vedotin was well tolerated with minimal systemic drug exposure and no local or systemic toxicities observed.

Embryo-fetal toxicity was observed in pregnant rats intravenously administered enfortumab vedotin or MMAE at clinically relevant systemic exposures. These toxicities are likely related to MMAE and not an effect of the anti-Nectin-4 antibody. Testicular toxicity was observed only in rats and was shown to be partially reversible by the end of a 24-week recovery period.

MMAE is genotoxic (aneugenic) by its intended pharmacological activity.

Refer to the current Investigator's Brochure for detailed nonclinical toxicology data.

2.2.1.3 Clinical Data

Enfortumab vedotin is currently being tested in multiple studies including phase 1, 2, and 3 studies, both as monotherapy and in combination with several anticancer therapies.

Safety data have been integrated from subjects who received single-agent enfortumab vedotin in the phase 3 study (EV-301), phase 2 study (EV-201) and 3 phase 1 studies (AGS-22M6E-11-1, EV-101, and EV-102). As of the dates of last evaluation for the completed studies (AGS-22M6E-11-1 [27 Apr 2015] and EV-102 [25 Feb 2019]) and the ISS data cutoff dates for ongoing studies EV-101 (17 Feb 2020), EV-201 (08 Sep 2020) and

EV-301 [15 Jul 2020], a total of 749 subjects had received at least 1 dose of enfortumab vedotin ranging from 0.5 to 1.25 mg/kg across the 5 studies. Of these, 680 subjects overall received enfortumab vedotin at the 1.25 mg/kg dose level. In this integrated safety population, 740 of 749 (98.8%) subjects experienced at least 1 TEAE and 701 (93.6%) subjects experienced a TEAE considered possibly or probably related to study drug by the investigator. Grade ≥ 3 TEAEs were experienced by 507 of 749 (67.7%) subjects overall. Grade ≥ 3 TEAEs considered possibly or probably related to study drug were observed in 354 of 749 (47.3%) subjects overall. Serious TEAEs were experienced by 336 of 749 (44.9%) subjects and 142 of 749 (19.0%) subjects experienced serious TEAEs considered possibly or probably related to study drug. TEAEs leading to study drug discontinuation (permanent withdrawal of study drug) were reported in 145 of 749 (19.4%) subjects and in 93 of these subjects (12.4% of subjects overall) the TEAE was considered as at least possibly related to study drug. Fifty (6.7%) subjects died due to a TEAE; in 14 (1.9%) of these subjects, TEAEs leading to death were assessed by the investigator as at least possibly related to study drug.

In the 1.25 mg/kg safety population, 673 of 680 (99.0%) subjects experienced at least 1 TEAE and 639 (94.0%) subjects experienced a TEAE considered possibly or probably related to study drug by the investigator. Grade ≥ 3 TEAEs were experienced by 468 (68.8%) subjects overall. Grade ≥ 3 TEAEs considered possibly or probably related to study drug were observed in 332 (48.8%) subjects overall. Serious TEAEs were experienced by 306 of 680 (45.0%) subjects and 132 (19.4%) subjects experienced serious TEAEs considered possibly or probably related to study drug. TEAEs leading to study drug discontinuation (permanent withdrawal of study drug) were reported in 126 (18.5%) subjects and, in 84 of these subjects (12.4% of subjects overall) the TEAE was considered at least possibly related to study drug. Forty-seven (6.9%) subjects died due to a TEAE; in 14 (2.1%) of these subjects, TEAEs leading to death were assessed by the investigator as at least possibly related to study drug.

In Study EV-301, a total of 608 subjects were randomized 1:1 to either enfortumab vedotin or chemotherapy treatment and 587 were dosed as of the 17 Dec 2020 data cutoff (296 subjects in the enfortumab vedotin arm and 291 subjects in the chemotherapy arm). In the enfortumab vedotin arm, 290 (98.0%) subjects have experienced at least 1 TEAE and 141 (47.6%) subjects have experienced at least 1 serious TEAE. In the chemotherapy arm, 288 (99.0%) subjects have experienced at least 1 TEAE and 131 (45.0%) subjects have experienced at least 1 serious TEAE.

In Study EV-901, a total of 26 subjects have received at least 1 infusion of enfortumab vedotin. All 26 (100%) subjects have experienced at least 1 TEAE and 11 (42.3%) subjects have experienced at least 1 serious TEAE.

Safety data observed to date in the current study EV-202 aligns with the known safety profile in the metastatic urothelial cancer (mUC) population and no new safety issues have been identified.

Population pharmacokinetic modeling demonstrated that dose adjustment is not warranted in subjects with mild, moderate or severe renal impairment nor subjects with mild hepatic impairment (the effect of moderate or severe hepatic dysfunction on the pharmacokinetics of enfortumab vedotin has not been assessed). The effect of end-stage renal disease, with or without dialysis, on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

Based on the safety data from clinical studies, the identified risks for enfortumab vedotin monotherapy are skin reactions (severe cutaneous adverse reactions [SCAR] and rash), hyperglycemia and pneumonitis/interstitial lung disease (ILD) (important identified risks); peripheral neuropathy, diarrhea/nausea/vomiting, extravasation events, dry eye (ocular disorders), neutropenia and anemia (identified risks); corneal disorders and blurred vision, IRRs other than extravasation events, ATAs, embryo-fetal toxicity and testicular toxicity (potential risks).

Efficacy analyses have shown that enfortumab vedotin demonstrates antitumor activity. In Study EV-101 (efficacy data cutoff: 25 Oct 2018), the confirmed ORR (complete response [CR] + partial response [PR]) in the metastatic UC 1.25 mg/kg dose group, was 42.9% (48 out of 112 subjects), including 5 subjects (4.5%) with CR and 43 subjects (38.4%) with PR. In Study EV-102 (date of last evaluation: 25 Feb 2019), the confirmed ORR was 35.3% (6/17 subjects). The majority of subjects had tumor shrinkage. In Study AGS-22M6E-11-1, (date of last evaluation: 27 Apr 2015), 9 subjects with various solid tumors were treated with enfortumab vedotin; 5 (55.6%) subjects achieved stable disease and 4 (44.4%) subjects had progressive disease. In Study EV-201 (data cutoff: 01 Mar 2019 for Cohort 1 and 08 Sep 2020 for Cohort 2), the confirmed ORR per blinded independent central review (BICR) assessment was 44% (55 of 125 subjects) in Cohort 1 (previously treated with a platinum-containing chemotherapy and a PD-1/PD-L1 inhibitor) and 52% (46 out of 89 subjects) in Cohort 2 (previously treated with a PD-1/PD-L1 inhibitor, platinum naïve and cisplatin ineligible). Per an FDA request, a later data cutoff date of 04 Dec 2020 was also used to provide an update to the DOR for Cohort 2 after all responders had been followed for at least 6 months from the onset of response. The updated confirmed ORR per BICR assessment was 51% (45 of 89 subjects); there was a loss of 1 responder when an equivocal new lesion identified at week 8 became unequivocal at a later time point. In Study EV-301 (data cutoff: 15 Jul 2020), the OS of subjects with locally advanced or metastatic UC treated with enfortumab vedotin was significantly prolonged on the enfortumab vedotin arm compared with the chemotherapy arm, with a 30% reduction in the risk of death (HR = 0.702, 95% CI: 0.556, 0.886; P = 0.00142, with a predetermined 1-sided significance level of 0.00679 based on the number of observed deaths). The median OS was 12.88 months for the enfortumab vedotin arm and 8.97 months for the chemotherapy arm.

In Study EV-103, Cohort K evaluated enfortumab vedotin and pembrolizumab combination treatment as first line therapy for cisplatin-ineligible subjects with locally advanced or metastatic urothelial cancer (data cutoff: 10 Jun 2022). In Cohort K, the confirmed ORR per BICR for subjects receiving enfortumab vedotin and pembrolizumab combination therapy was 64.5% (49 of 76 subjects), including 8 subjects (10.5%) with CR and 41 subjects (53.9%) with PR. Activity was seen regardless of PD-L1 expression level, and the

combination treatment was tolerable with a manageable safety profile [Rosenberg et al, 2022].

A summary of the clinical and nonclinical safety data and efficacy data relevant to the enfortumab vedotin and its study in human subjects are provided in the Investigator's Brochure. Based upon the totality of the safety data available, the observed safety profile supports further clinical development of enfortumab vedotin in the tumors selected for this study.

2.2.2 Summary of Key Safety Information for Enfortumab Vedotin

As of the data cutoff for Enfortumab vedotin IB Edition 12 (17 Dec 2022), 1220 subjects had been treated with EV in studies AGS-2M6E-11-1, EV-101, EV-102, EV-103, EV-201, EV-202, EV-203 and EV-301. AEs of interest for EV are based on current safety data from clinical studies and known risks with similar ADCs. The important identified risks for EV are skin reactions (severe cutaneous adverse reactions and rash), hyperglycemia and pneumonitis/ILD. Other identified risks are extravasation events, peripheral neuropathy, diarrhea/nausea/vomiting, dry eye (ocular disorders), neutropenia and anemia. The potential risks are corneal disorders and blurred vision (ocular disorders), IRRs (other than extravasation events), ATAs, embryo-fetal toxicity and testicular and ovarian toxicity.

Please refer to the current Investigator's Brochure for further details.

2.3 Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the pembrolizumab Investigator's Brochure.

Refer to the pembrolizumab Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

2.3.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating

lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Hunder et al, 2008; Dudley et al, 2005].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [Greenwald et al, 2005; Okazaki et al, 2001].

The structure of murine PD-1 has been resolved [Zhang et al, 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Riley, 2009; Chemnitz et al, 2004; Sheppard et al, 2004; and Okazaki et al., 2001]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Francisco et al, 2010; Parry et al, 2005].

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities [Spranger et al, 2014; Curran et al, 2010; Pilon-Thomas et al, 2010; Weber, 2010; Hirano et al, 2005; Blank et al, 2004; Strome et al, 2003;]. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma [Curran et al, 2010; Pilon-Thomas et al, 2010; Nomi et al, 2007; Zhang et al, 2004; Strome, 2003]. In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo [Curran et al, 2010]. Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the pembrolizumab IB).

2.4 Study Rationale

In cohorts 1 to 8, enfortumab vedotin will be administered at a dose of 1.25 mg/kg as an intravenous on days 1, 8 and 15 of each 28-day cycle. This dose and regimen has demonstrated an acceptable safety profile and encouraging clinical activity in the phase 1 and 2 studies in subjects with urothelial cancer. The tumors selected for this study were based on Nectin-4 expression, nonclinical data, sensitivity to microtubule inhibition, incidence rate and potential unmet clinical need.

A phase 1 dose escalation and expansion study (EV-101) with enfortumab vedotin monotherapy in subjects with metastatic urothelial cancer and other malignant solid tumors demonstrated encouraging antitumor activity. Enfortumab vedotin provided durable responses and meaningful survival results in subjects after anti-PD-(L)-1 therapy in a population with a high unmet medical need. The confirmed ORR by central review was 45% in subjects with urothelial cancer [Rosenberg et al, 2019]. The median OS of 12.3 months is encouraging given the historical median OS is ≤ 10.3 months [Bellmunt et al, 2017].

Study EV-102 is an open-label, randomized, dose escalation study assessing safety, tolerability and pharmacokinetics of enfortumab vedotin in Japanese subjects with locally advanced or metastatic urothelial cancer. Enfortumab vedotin at a dose of 1.25 mg/kg was safe and generally well tolerated in Japanese subjects with locally advanced or metastatic urothelial cancer. Pharmacokinetic profiles and clinical responses (ORR 35%; disease control rate [DCR] 77%) of enfortumab vedotin were encouraging and consistent with reports in a North American population.

In a pivotal phase 2 study (EV-201) [Petrylak et al, 2019], urothelial cancer subjects must have had prior treatment with platinum-containing chemotherapy or be platinum-naïve and ineligible for cisplatin treatment. The results for this study demonstrated that enfortumab vedotin was the first novel therapeutic to demonstrate substantial clinical activity in subjects who progressed after platinum chemotherapy and a PD-1/L1 inhibitor. The confirmed ORR was 44% in subjects treated with enfortumab vedotin 1.25 mg/kg. The median OS was 11.7 months and the median DOR was 7.6 months. These results are highly consistent with the phase 1 EV-101 trial in the same subject population.

Phase 3 study EV-301 enrolled 608 subjects with locally advanced or metastatic urothelial cancer who received prior PD-1 or PD-L1 inhibitor and platinum-based chemotherapy. The primary efficacy endpoint of overall survival was 12.9 months in the EV arm versus 9 months for those receiving chemotherapy. Median PFS was 5.6 months compared with 3.7 months, respectively. The ORR was 40.6% versus 17.9%, respectively.

Immunohistochemical studies have demonstrated expression of Nectin-4 and Nectin-4 mRNA on a variety of tumor types including, but not limited to, bladder, breast, pancreatic and lung. In vitro pharmacology studies have demonstrated specific high affinity binding of AGS-22M6E and AGS-22M6 (unconjugated antibody) to Nectin-4 expressed on human cancer cells [Challita-Eid et al, 2016].

Given the broad expression of Nectin-4 across a variety of tumors and the activity seen to date in urothelial cancer, the sponsor has identified additional tumors to evaluate enfortumab vedotin including breast, lung, head and neck, gastric, GEJ, and esophageal cancers. Nectin-4 expression is not an inclusion requirement in this study because it is typically prevalent in these tumor types. However, Nectin-4 expression will be assessed retrospectively.

This study is designed to assess the safety and antitumor activity of enfortumab vedotin monotherapy in these selected tumors. In addition, the study will identify the efficacy signal with enfortumab vedotin in well-defined patient populations.

The tumors selected for the current study (breast, lung, head and neck, gastric, GEJ, and esophageal cancer) are representative of tumors with moderate to high Nectin-4 expression, and for which there is a need to improve outcomes in the advanced and treatment refractory setting. Furthermore, the supportive preclinical sensitivity to enfortumab vedotin, along with the clinical data, and evidence based on published literature provide support for the current study. Cohort 6 was designed as a mixed population of subjects with gastric, GEJ, and esophageal cancers. Consistent with current clinical practice guidelines regarding standard of care treatment for different histologies of gastroesophgeal cancers, in Amendment 2, all subjects enrolled into Cohort 6 under protocol versions 1 and 2 are reallocated to 2 cohorts based on tumor histology: Cohort 7, which will comprise subjects with gastric cancer, esophageal adenocarcinoma and GEJ adenocarcinoma and Cohort 8, which will comprise subjects with esophageal squamous cell carcinoma (ESCC). Each cohort will continue to enroll and be assessed according to the guidance provided in [Section 4 Study Design].

2.4.1 Rationale for Cohort 9 – Enfortumab Vedotin and Pembrolizumab in Combination

Pembrolizumab demonstrated effective antitumor activity as a single agent in KEYNOTE-048 in subjects with metastatic or unresectable, recurrent HNSCC whose tumors express PD-L1 (CPS $\geq$ 1), and it is approved for use as monotherapy in both first-line and second-line HNSCC [Burtness et al, 2019]. Although the approval of pembrolizumab in this patient population represents a significant advancement in the treatment of HNSCC, patients with recurrent/metastatic HSNCC continue to have poor prognosis and limited durability of response with the currently available standard of care [Burtness et al, 2019].

The primary analysis of EV-202 cohort 5 was completed on 27 Jul 2022, and the number of subjects with confirmed responses exceeded the protocol pre-specified minimum number of responders to claim promising antitumor activity. Cohort 5 enrolled 46 subjects (30 North American, 16 Japanese; 40 were male) who had each received prior treatment with platinum-containing chemotherapy and a PD-1/PD-L1 inhibitor. The cORR (per Investigator assessment) for the cohort was 23.9%, including 1 subject with a CR and 10 subjects with PR, with a median duration of response of 9.4 months (median DOR was reached approximately 3 months after primary analysis). DCR (per Investigator assessment) was 56.5%. The safety data observed in cohort 5 were consistent with the known safety profile of

enfortumab vedotin, and no new safety signals were identified. These data suggest that enfortumab vedotin has promising antitumor activity in recurrent/metastatic HNSCC.

Preclinical studies of vedotin ADCs, including enfortumab vedotin, show that these ADCs induce hallmarks of immunogenic cell death, including the release of damage-associated molecular patterns which ultimately may lead to engulfment of tumor cells by antigen-presenting cells and subsequent cross-presentation of tumor antigens to cytotoxic T cells. These T cells mount antigen-specific responses that are further augmented by PD1/PD-L1 inhibitors, such as pembrolizumab [Hoimes, 2023]. Thus, combining enfortumab vedotin with pembrolizumab may enhance antitumor activity versus either agent alone on the basis of their distinct and complementary engagement of the immune system.

In the EV-103 study, combination therapy of enfortumab vedotin and pembrolizumab demonstrated compelling efficacy in first line cisplatin-ineligible subjects with locally advanced/mUC, resulting in rapid and durable responses, with a manageable safety profile. These data suggest that the combination of enfortumab vedotin and pembrolizumab may have the potential to improve patient outcomes better as compared to the use of either agent alone.

As discussed above, clinical trials in HNSCC such as KEYNOTE-040 and KEYNOTE-048 have demonstrated that the PD 1/PD-L1 pathway is an effective target for therapeutic intervention in HNSCC [Burtness et al, 2019].

Based on the demonstrated efficacy of pembrolizumab in R/M HNSCC and the observed antitumor activity of enfortumab vedotin in HSNCC in the current study, and the favorable benefit/risk profile of the combination of enfortumab vedotin and pembrolizumab in the EV103 study, it is hypothesized that combination therapy with enfortumab vedotin and pembrolizumab may have potential as a first-line treatment in PD-L1 positive patients with R/M HNSCC.

2.5 Risk/Benefit Assessment

Subjects with locally advanced or metastatic cancer selected for this study have cancer that recurred or progressed following standard of care therapy and have limited treatment options. Nonclinical and clinical data to date support a favorable benefit/risk ratio for enfortumab vedotin in subjects with urothelial cancer and supports further exploration of the use of enfortumab vedotin in other locally advanced or metastatic cancers including breast, lung, head and neck, gastric, GEJ, and esophageal cancer.

The identified and potential risks associated with enfortumab vedotin are outlined in the [Sections 2.2.1.2, 2.2.1.3 and 2.2.2], and the enfortumab vedotin Investigator's Brochure. Evidence of clinical activity in locally advanced or metastatic urothelial carcinoma has been observed in other single-arm studies of enfortumab vedotin (described in [Section 2.2.1.3 Clinical Data]) and this may translate into an improvement in outcome for the tumors selected for this trial. However, there may still be no direct benefit to subjects participating in the current clinical study.

For each cohort, one interim analysis is planned to assess the antitumor activity for that cohort and a decision rule will be in place in order to not expose subjects to an ineffective treatment. A Bayesian optimal design for Phase 2 [Zhou et al, 2017] will be used to guide the interim decision rule [Section 9.11 Interim Analysis].

To assure an ongoing favorable benefit/risk assessment for subjects enrolled into the study, a Safety Monitoring Committee (SMC) will be utilized to monitor safety data as described in [Section 10.4.1 Safety Monitoring Committee].

2.5.1 Risk/Benefit Assessment for Combination of Enfortumab Vedotin and Pembrolizumab

Pembrolizumab has a positive benefit/risk profile and is well tolerated in the approved indications. Publications of a significantly positive benefit/risk ratio have been reported for melanoma in a single arm study encompassing nearly 1000 subjects (KEYNOTE -001), which led to US FDA approval in September 2014. Pembrolizumab has subsequently received approval for the treatment of patients with NSCLC and for the treatment of patients with R/M HNSCC. In 2019, pembrolizumab received FDA approval for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC. Pembrolizumab was approved for use in combination with platinum and fluorouracil (FU) for all patients and as a single agent for patients whose tumors express PD-L1 (CPS ≥1). The approval was based on the results of the KEYNOTE-048 trial in which subjects were randomized (1:1:1) to receive one of the following treatments: pembrolizumab as a single agent; pembrolizumab, carboplatin or cisplatin, and FU; or cetuximab, carboplatin or cisplatin, and FU.

The KEYNOTE-048 trial demonstrated a statistically significant improvement in OS in the overall population for subjects randomized to pembrolizumab plus chemotherapy compared with cetuximab plus chemotherapy at a pre-specified interim analysis. The median OS for the CPS ≥ 1 subgroup was 13.6 months for the pembrolizumab plus chemotherapy arm and 10.4 months for the cetuximab plus chemotherapy arm (HR 0.65; 95% CI: 0.53, 0.80; p = 0.00002). Results were similar in the CPS ≥ 20 subgroup with median OS 14.7 vs 11.0 months (HR 0.60; 95% CI: 0.45, 0.82).

The trial also demonstrated statistically significant improvements in OS for the subgroups of subjects with PD-L1 CPS ≥1 HNSCC and PD-L1 CPS ≥ 20 HNSCC randomized to pembrolizumab as a single agent compared with cetuximab plus chemotherapy. In the CPS ≥ 1 subgroup, the median OS was 12.3 months for the pembrolizumab arm and 10.3 months for the cetuximab plus chemotherapy arm (HR 0.78; 95% CI: 0.64, 0.96; p = 0.0171). For the CPS ≥20 subgroup, the median OS was 14.9 months for the pembrolizumab arm and 10.7 months for the cetuximab plus chemotherapy arm (HR 0.61; 95% CI: 0.45, 0.83; p = 0.0015). At the time of the interim analysis, there was no significant difference in OS between the pembrolizumab as a single agent arm and the cetuximab plus chemotherapy arm for the overall population.

There were no significant differences in progression-free survival for either pembrolizumab-containing arm compared to the cetuximab plus chemotherapy arm in any population.

While evidence of activity in this indication have been observed in the current study, there may still be no direct benefit to subjects participating in this cohort. Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying iBs and Informed Consent documents.

The most common adverse reactions reported in ≥ 20% of subjects who received pembrolizumab as a single agent in KEYNOTE-048 were fatigue, constipation, and rash. In KEYNOTE-048, pembrolizumab was discontinued for adverse reactions in 12% of subjects in the pembrolizumab single agent arm. The most common adverse events resulting in permanent discontinuation of pembrolizumab were sepsis (1.7%) and pneumonia (1.3%). Adverse events leading to the interruption of pembrolizumab occurred in 31% of subjects; the most common adverse events leading to interruption of pembrolizumab (≥ 2%) were pneumonia (2.3%), pneumonitis (2.3%) and hyponatremia (2%) [KEYTRUDA Prescribing Information, Merck Sharp & Dohme LLC, 2021].

The most common adverse reactions reported in ≥ 20% of subjects who received pembrolizumab in combination with chemotherapy in KEYNOTE-048 were nausea, fatigue, constipation, vomiting, mucosal inflammation, diarrhea, decreased appetite, stomatitis, and cough.

The recommended pembrolizumab dose for HNSCC is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in subjects without disease progression.

The combination of enfortumab vedotin and pembrolizumab has demonstrated efficacy in previously untreated cisplatin ineligible subjects with locally advanced or metastatic urothelial cancer in Cohort K of study EV-103. In this study, a total of 149 subjects were treated (76 subjects were treated with the combination and 76 subjects received enfortumab vedotin monotherapy). The confirmed ORR for the combination of enfortumab vedotin plus pembrolizumab was 64.5% (95% CI 52.7, 75.1). The median DOR was not reached [Rosenberg et al, 2022].

TEAEs of special interest included skin reactions (EV+P, n = 51 [67.1%]; EV, n = 33 [45.2%]), peripheral neuropathy (EV+P, n = 46 [60.5%]; EV, n = 40 [54.8%]), ocular disorders (e.g., dry eye and blurred vision; EV+P, n = 20 [26.3%]; EV, n = 21 [28.8%]) and hyperglycemia (EV+P, n = 11 [14.5%]; EV, n = 8 [11.0%]). The majority of treatment related AESIs were grade ≤ 2. [Rosenberg et al, 2022]. The safety profile was generally consistent with the known profile for EV+P. EV monotherapy was consistent with prior experience.

The potential for overlapping toxicities in the combination of enfortumab vedotin and pembrolizumab is recognized by the sponsors and carefully monitored. In many cases it is not possible to attribute causality clearly to one agent or the other. The sponsors' approach has

been to compare the emerging combination safety data to the known safety profile of each agent, also taking into consideration what is known about the mechanism of toxicity. Subjects receiving the combination of enfortumab vedotin and pembrolizumab have experienced identified risks observed with monotherapy enfortumab vedotin which include: pneumonitis, skin reactions (SCAR and rash), hyperglycemia, peripheral neuropathy, neutropenia, anemia, gastrointestinal symptoms (nausea, vomiting and diarrhea), and extravasation site reactions. Subjects with mUC receiving the combination of enfortumab vedotin and pembrolizumab have also experienced potential risks observed with enfortumab vedotin monotherapy which include: ocular toxicity (blurred vision and corneal disorders). These risks should be managed according to the guidance described in the protocol.

Immune-mediated adverse events (imAEs) known to occur with PD-1/PD-L1 inhibitors were observed. The protocol-defined adverse event of interest category of imAEs was specific to the EV-103 study for treatment with enfortumab vedotin in combination with the PD-1 inhibitor pembrolizumab and was aligned with the pembrolizumab search strategy.

imAEs associated with pembrolizumab exposure 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 regarding imAEs associated with pembrolizumab, most were reversible and could be managed with an interruption of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected imAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and/or skin biopsy may be included as part of the evaluation. Based on the severity of imAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose delay and toxicity management guidelines for imAEs associated with pembrolizumab are provided in the pembrolizumab package insert and IB.

Reported events in EV-103 appear consistent with immune events reported with checkpoint inhibitors and no new safety signals have been observed. To assure a favorable risk-benefit balance for subjects enrolled in cohort 9, careful monitoring by the safety monitoring committee will continue.

3 STUDY OBJECTIVE(S) AND ENDPOINT(S)

The primary, secondary and exploratory objectives and endpoints for this study are listed in [Table 5] and [Table 6].

Table 5 Cohorts 1 to 8 Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
• To determine the antitumor activity of enfortumab vedotin as measured by confirmed ORR per investigator assessment	• Confirmed ORR (complete response [CR] + PR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 as determined by investigator
Secondary	
• To assess other measures of antitumor activity of enfortumab vedotin per investigator assessment	• DOR per RECIST Version 1.1 per investigator assessment • DCR (CR + PR + stable disease [SD]) per RECIST Version 1.1 per investigator assessment • PFS per RECIST Version 1.1 by investigator assessment
• To assess the OS	• OS
• To assess the safety and tolerability of enfortumab vedotin	• Safety variables o Adverse events (AEs) o Laboratory tests o Vital sign measurements o 12-lead electrocardiogram o Eastern Cooperative Oncology Group (ECOG) performance status
Exploratory	
• To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome, including Nectin-4 expression	• Exploratory genomic and/or other biomarkers that may correlate with treatment outcome, including Nectin-4 expression
• To assess the pharmacokinetics of enfortumab vedotin and MMAE	• Selected pharmacokinetic parameters of enfortumab vedotin and MMAE
• To assess the immunogenicity of enfortumab vedotin	• Incidence of antitherapeutic antibodies (ATA) to enfortumab vedotin
• To evaluate the treatment effect of enfortumab vedotin on quality of life (QOL)	• PRO per EuroQOL 5-dimensions (EQ-5D-5L) and global pain assessment (worst pain in the last 24 hours)
• To assess measures of antitumor activity of enfortumab vedotin per blinded independent central review (BICR)	• Response related endpoints per BICR

Table 6 Cohort 9 Objective(s) and Endpoint(s)

Objective(s)	Endpoint(s)
Primary	
• To determine the antitumor activity of enfortumab vedotin in combination with pembrolizumab	• Confirmed ORR (CR + PR) per RECIST Version 1.1 as determined by investigator
Secondary	
• To assess other measures of antitumor activity of enfortumab vedotin in combination with pembrolizumab per investigator assessment	• DOR per RECIST Version 1.1 by investigator assessment • DCR (CR + PR + SD) per RECIST Version 1.1 by investigator assessment • PFS per RECIST Version 1.1 by investigator assessment
• To assess the OS of enfortumab vedotin in combination with pembrolizumab	• OS
• To assess the safety and tolerability of enfortumab vedotin in combination with pembrolizumab	• Safety variables o AEs o Laboratory tests o Vital sign measurements o 12-lead electrocardiogram o ECOG performance status
Exploratory	
• To evaluate potential genomic and/or other biomarkers that may correlate with treatment outcome, including Nectin-4 expression	• Exploratory genomic and/or other biomarkers that may correlate with treatment outcome, including Nectin-4 expression
• To assess the pharmacokinetics of enfortumab vedotin and MMAE	• Selected pharmacokinetic parameters of enfortumab vedotin and MMAE
• To assess the immunogenicity of enfortumab vedotin	• Incidence of ATA to enfortumab vedotin
• To evaluate the treatment effect of enfortumab vedotin in combination with pembrolizumab on QOL	• PRO per EORTC QLQ H&N43, global pain assessment (worst pain in the last 24 hours), FACT-G question G05 and symptom-specific questions from PRO-CTCAE
• To assess measures of antitumor activity of enfortumab vedotin in combination with pembrolizumab per BICR	• ORR, DOR, DCR and PFS per RECIST Version 1.1 by BICR
• To assess measures of antitumor activity of enfortumab vedotin in combination with pembrolizumab per modified RECIST v1.1 for immune-based therapeutics (iRECIST)	• ORR, DOR, DCR and PFS per iRECIST by investigator assessment

4 STUDY DESIGN AND DOSE RATIONALE

4.1 Study Design

This is an open-label, multicenter, multicohort, phase 2 study designed to assess the antitumor activity and safety of enfortumab vedotin as a single agent (cohorts 1 to 8) and in combination with pembrolizumab (cohort 9) in adult subjects with locally advanced or metastatic malignant solid tumors. Approximately 40 subjects will be enrolled into each of the following cohorts in a 2 stage design.

- Cohort 1: HR+/HER2- breast cancer; or
- Cohort 2: TNBC; or
- Cohort 3: Squamous NSCLC; or
- Cohort 4: Non-squamous NSCLC; or
- Cohort 5: Head and neck cancer; or
- Cohort 6: Gastric or GEJ or esophageal cancer (reallocated to Cohorts 7 or 8)
- Cohort 7: Gastric and EAC including GEJ adenocarcinoma
- Cohort 8: ESCC
- Cohort 9: First-line HNSCC

Subjects enrolled into Cohort 6 will be reallocated based on disease type and histology into Cohorts 7 or 8.

For each cohort, one interim analysis is planned to assess the antitumor activity for that cohort. The interim analysis will be performed for a given cohort at the time when 20 subjects are evaluable for tumor response per investigator assessment following study treatment. A Bayesian optimal design for phase 2 (BOP2) [Zhou et al, 2017] is used to guide interim decision rule. For each cohort, based on the 2-stage BOP2 design, when the number of subjects with confirmed response (CR and PR) is less than the prespecified minimum number of responders at stage 1, the enrollment of the cohort may stop; otherwise, the enrollment will continue into Stage 2 until the planned size of the cohort is reached.

In cohorts 1 to 8, subjects will receive enfortumab vedotin at a dose of 1.25 mg/kg as an intravenous infusion on days 1, 8 and 15 of each 28-day cycle.

In cohort 9, subjects will receive enfortumab vedotin 1.25 mg/kg on days 1 and 8 and pembrolizumab 200 mg on day 1 of each 21-day cycle.

For each subject, the study will consist of 3 periods: screening/baseline, treatment and follow-up. The screening/baseline period will take place up to 28 days prior to the first dose of study treatment. For cohort 9, a local PD-L1 test result may be used for eligibility. A PD-L1 CPS $\geq$ 1 is required for enrollment. An archival tumor sample will be submitted from each subject for central PD-L1 and other biomarker testing. If archival tumor tissue for central PD-L1 testing is insufficient or not available, a biopsy will be performed to obtain a tumor sample for central testing.

In the treatment period, starting at cycle 1, subjects in cohorts 1 to 8 will receive enfortumab vedotin on days 1, 8, and 15 every 28-day cycle until one of the treatment discontinuation

criteria are met. Subjects in cohort 9 will receive enfortumab vedotin on days 1 and 8 and pembrolizumab on day 1 of each 21-day cycle until a discontinuation criteria is met.

For cohorts 1 to 8, imaging scan and disease assessment will be performed at screening/baseline and repeated every 8 weeks (56 days ± 7 days) from the first dose of study treatment throughout the study until the subject has radiologically-confirmed disease progression, initiates a new subsequent anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first. After 1 year on study treatment, the frequency of disease assessment will be reduced to every 12 weeks (84 days ± 7 days). Subjects in cohorts 1 to 8 who discontinue study treatment for reasons other than radiologically-confirmed disease progression by RECIST Version 1.1 will enter into a post treatment follow-up period and continue to receive imaging scans every 8 weeks (56 days ± 7 days) until the subject has radiologically-confirmed disease progression, initiates a new anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first.

In cohort 9, the first on-study imaging and disease assessment will be performed 9 weeks (63 days ± 7 days) from the first dose of study treatment and then every 6 weeks (42 days ± 7 days) throughout the study until the subject has radiologically-confirmed disease progression (iCPD per iRECIST), initiates a new subsequent anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first. Subjects in cohort 9 with unconfirmed progressive disease per iRECIST guidelines [Seymour et al, 2017] who are clinically stable may continue on study treatment until progression is confirmed by the investigator (iCPD) at the next imaging assessment 6 weeks (± 7 days) after iUPD. Treatment with pembrolizumab will be discontinued once the subject has received a maximum of 35 administrations of pembrolizumab (approximately 2 years).

Subjects in cohort 9 who discontinue study treatment (both enfortumab vedotin and pembrolizumab) for reasons other than radiologically confirmed disease progression per iRECIST will enter into a post treatment follow-up period and have physical exams, ECOG and disease assessments every 6 weeks (± 7 days) up to 18 months after first dose, then every 9 weeks (± 7 days) until the subject has radiologically confirmed disease progression per iRECIST as determined by the investigator, initiates a subsequent anticancer therapy, dies, withdraws consent, or the study closes. During study treatment, palliative radiotherapy on a nontarget lesion that is not progressing will not be considered a subsequent anticancer therapy; however, radiotherapy on any target lesion will be a subsequent anticancer therapy.

Copies of all imaging scans will also be sent to the independent review facility in a timely manner. Images at the independent review facility will be stored. Imaging scans for a cohort may be read at the independent review facility when the minimum number of responders per investigator assessment (subjects with confirmed CR and PR) to claim promising antitumor activity at stage 1 are met based on the 2-stage BOP2 design. Central images may also be read in certain circumstances as determined by the sponsor.

An end of treatment (EOT) visit will be performed within 7 days after the last dose of enfortumab vedotin or the decision to discontinue treatment, or prior to initiation of another

anticancer therapy, whichever occurs earlier. This will be followed by a 30-day safety follow-up to be completed 30 days (+ 7-day window) from the last dose of enfortumab vedotin. The 30-day follow-up assessments should be completed prior to the initiation of another anticancer therapy.

After radiologically-confirmed disease progression or initiation of subsequent anticancer therapy, whichever occurs first, subjects will be contacted every 12 weeks in the long-term follow-up period for survival status until death, withdrawal of consent, lost to follow-up or study closure, whichever occurs first. Telephone contact with the subject is sufficient in the long-term follow-up period unless any assessment must be repeated to confirm resolution of drug-related AEs.

Confirmed ORR per investigator assessment is the primary endpoint. Confirmed ORR is defined as the proportion of subjects whose objective response is confirmed CR or PR according to RECIST Version 1.1. Response (CR or PR) must be confirmed with a repeat imaging scan 4 weeks (28 days + 7-day window) after first response.

Blood samples for pharmacokinetics and ATA will be collected at protocol-specified time points. Validated assays will be used to measure the concentrations of enfortumab vedotin and MMAE in serum or plasma and to assess ATA. Samples for exploratory biomarkers will be collected at protocol-specified time points. Enfortumab vedotin biomarker assessments will not be used for subject selection.

4.2 Dose Rationale

4.2.1 Enfortumab Vedotin

In cohorts 1 to 8, subjects will receive enfortumab vedotin at a dose of 1.25 mg/kg as an intravenous infusion on days 1, 8 and 15 of each 28-day cycle. This dose and regimen has demonstrated an acceptable safety profile and encouraging clinical activity in the phase 1 study (EV-101 [ASG-22CE-13-2]), the phase 2 study (EV-201) and the phase 3 study (EV-301).

The phase 1 study (EV-101) evaluated escalating dose levels of 0.5, 0.75, 1 and 1.25 mg/kg, with expansion cohorts at the 0.75, 1, and 1.25 mg/kg dose levels. A maximum tolerated dose (MTD) was not reached in this study. At the 1 mg/kg dose level, 2 dose-limiting toxicities (DLTs) were observed: grade 3 proctalgia (later changed to grade 2 by the investigator) thought related to radiation recall and grade 4 hyperuricemia without clinical sequelae. No DLT was observed at 1.25 mg/kg and doses above 1.25 mg/kg were not tested.

EV-201 is a single-arm study of enfortumab vedotin (1.25 mg/kg intravenously on days 1, 8, and 15 of every 28-day cycle) in subjects with urothelial carcinoma from the US and Japan. Results from this study were consistent with the EV-101 study. AEs in cohort 1 (n = 125) were consistent with those previously reported in enfortumab vedotin clinical development program.

EV-301 (7465-CL-0301) is a phase 3 study evaluating the safety and efficacy of enfortumab vedotin given as monotherapy on days 1, 8 and 15 of each 28-day cycle versus chemotherapy

in subjects with locally advanced or metastatic UC who were previously treated with chemotherapy and PD-1/PD-L1 inhibitors. The observed safety and efficacy results of EV-301 further support the 1.25 mg/kg dose regimen.

Incidence of some of the most frequent drug-related AEs, such as diarrhea and rash, although primarily grades 1 to 2 and clinically manageable, increased with increasing dose levels. Moreover, dose reductions due to AEs were more frequent for the 1.25 mg/kg vs lower dose levels. Safety assessments of both metastatic urothelial cancer subjects and nonmetastatic urothelial cancer subjects showed that frequency of all TEAEs, AEs leading to withdrawal, and grade 3 to 4 TEAEs were comparable across all dose levels.

While all doses of enfortumab vedotin demonstrated activity, the 1.25 mg/kg dose was associated with the highest activity and had an acceptable safety profile.

Enfortumab vedotin exposure response analyses of best overall response (BOR), PFS and OS outcomes suggested an apparent efficacy plateau at higher systemic exposure levels for subjects in exposure quartiles Q2 to Q4, therefore, further increases in enfortumab vedotin exposures at doses greater than 1.25 mg/kg may not provide additional benefit. Although logistic regression analyses revealed relationships between enfortumab vedotin exposure and some reported safety outcomes, treatment with 1.25 mg/kg enfortumab vedotin was associated with a manageable safety profile across the entire range of concentrations in subjects who had received a platinum containing chemotherapy in the locally advanced or metastatic setting [7465-PK-0004].

In summary, the dose regimen of 1.25 mg/kg on days 1, 8 and 15 of each 28-day cycle proposed for cohorts 1 to 8 of this study has demonstrated an acceptable safety profile and encouraging clinical activity that was higher than at lower dose levels.

In cohort 9, subjects will receive enfortumab vedotin at the 1.25 mg/kg dose on days 1 and 8 of each 21-day cycle. Justification for this dose includes the following:

- PK analysis from the EV-103 study indicates when comparing the same dose level the average weekly total exposure of enfortumab vedotin following administration on days 1 and 8 of a 21-day cycle is similar to that observed for dosing on days 1, 8 and 15 of a 28-day cycle.
- Clinical data from EV-103 cohorts A and K indicated efficacy in the mUC population with this dosing schedule
- Safety data from EV-103 shows this combination dosing schedule to be tolerable and consistent with the AE profiles for each individual agent.

4.2.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to

10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5 fold exposure range (refer to the pembrolizumab IB)

- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit/risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3 End of Study Definition

The study start is defined as the date the first subject signs informed consent. End of the study is defined as the last visit or scheduled procedure shown in schedules of assessments for the last subject in the study. The study will be closed 5 years after enrollment of the last subject, or when no subjects remain in long-term follow-up, whichever occurs first. Additionally, the sponsor may terminate the study at any time.

5 STUDY POPULATION

The study population will consist of subjects with locally advanced or metastatic malignant solid tumors, including:

- HR+/HER2- breast cancer; or
- TNBC; or
- Squamous NSCLC; or
- Non-squamous NSCLC; or
- Head and neck cancer/HNSCC; or
- Gastric or GEJ or esophageal cancer

All screening assessments must be completed and reviewed by the investigator to confirm the potential subject meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) will not be granted.

5.1 Inclusion Criteria

Subject 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 subject prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation at the time of signing the informed consent form (ICF).
3. Subject has measurable disease by RECIST Version 1.1.
4. Subject has accessible archival tumor tissue from either the primary tumor or a metastatic site, for which source and availability have been confirmed prior to study treatment. If no archival tumor tissue is available, the subject will have a biopsy to obtain tumor tissue prior to study treatment. If the subject is unable to undergo a biopsy due to safety concerns, enrollment into the study must be discussed with the medical monitor.
    a. For cohort 9 only: Subject should submit archival or fresh tumor tissue sample for PD-L1 central testing during screening if no local PD-L1 test result is available. Central test result for PD-L1 will be required prior to subject enrollment. For cohort 9 subjects with local PD-L1 test result confirming CPS $\geq$ 1, archival or

fresh tissue sample for exploratory analysis should be submitted within 5 days of enrollment.

5. Subject has ECOG performance status of 0 or 1.
6. Subject has the following baseline laboratory data. If a subject has received a recent blood transfusion, the hematology tests must be obtained ≥ 28 days after any blood transfusion.
   - absolute neutrophil count (ANC) ≥ 1.0×10^9/L
   - platelet count ≥ 100×10^9/L
   - hemoglobin ≥ 9 g/dL
   - serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease
   - creatinine clearance (CrCl) ≥ 30 mL/min as estimated per institutional standards or as measured by 24-hour urine collection (glomerular filtration rate [GFR] can also be used instead of CrCl).
   - Cohorts 1-8: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN
   - Cohort 9: ALT and AST ≤ 2.5 × ULN (≤ 5 × ULN for subjects with liver metastases)
7. Female subject is not pregnant (see [Appendix 12.3 Contraception Requirements]) and at least 1 of the following conditions apply:
   a. Not a woman of childbearing potential (WOCBP) (see [Appendix 12.3 Contraception Requirements])
   b. WOCBP who agrees to follow the contraceptive guidance (see [Appendix 12.3 Contraception Requirements]) from the time of informed consent through at least 6 months after the last dose of study treatment administration
8. Female subject must agree not to breastfeed starting at screening and throughout the study period and for 6 months after the last dose of study treatment administration.
9. Female subject must not donate ova starting at first dose of study treatment and throughout the study period and for 6 months after the last dose of study treatment administration.
10. Male subject with female partner(s) of childbearing potential (including breastfeeding partner) must agree to use contraception (see [Appendix 12.3 Contraception Requirements]) throughout the treatment period and for 6 months after the last dose of study treatment administration.
11. Male subject must not donate sperm during the treatment period and for 6 months after the last dose of study treatment administration.
12. Male subject with pregnant partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy throughout the study period and for 6 months after the last dose of study treatment administration.
13. Subject agrees not to participate in another interventional study while receiving study treatment in the present study.

Disease Specific Inclusion Criteria:

A line of therapy is defined as a course of treatment at the end of which there was disease progression, toxicity, or in the investigator's opinion, maximum benefit has been achieved. If the subject discontinued therapy due to any other reason but progressed without receiving other treatment, this would be considered a line of therapy.

Cohort 1: HR+/HER2- breast cancer

14. Subject has evidence of radiographic progression on or after the last regimen received.
15. Subject has histologically or cytologically-confirmed HR+/HER2- (estrogen receptor [ER] positive and/or progesterone receptor [PR] positive, and HER2 negative) breast cancers and are not considered a candidate for further hormonal therapy. Subject will be considered HR+ if biopsies show ≥ 1% expression of ER or PR as per current American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.
16. Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
17. Subject must have received a taxane or anthracycline in the neoadjuvant, adjuvant or incurable, locally advanced or metastatic setting.
    - Prior cytotoxic regimen received in the neoadjuvant or adjuvant setting will count as a prior cytotoxic regimen if disease recurrence occurred during or within 6 months of completing the regimen.
18. Subject has progressed, relapsed, or discontinued for toxicity during or after at least 1 prior standard of care cytotoxic regimen in the incurable, unresectable locally advanced or metastatic setting, and has not received > 2 prior lines of cytotoxic therapy in the locally advanced or metastatic setting. No limit applies to endocrine therapies. Poly(ADP-ribose) polymerases (PARP) inhibitors do not count as a line of cytotoxic therapy.
19. Subject has progressed, relapsed, or discontinued for toxicity during or after receiving endocrine therapy or with hormonally-directed therapy with cyclin-dependent kinase (CDK) inhibitors. Prior therapy with CDK inhibitors is not required.

Cohort 2: triple negative breast cancer

20. Subject has evidence of radiographic progression on or after the last regimen received.
21. Subject has histologically or cytologically-confirmed TNBC; defined as unequivocal TNBC histology (ER-negative/PR-negative/HER2-negative). This is defined by < 1% expression of ER and PR by immunohistochemistry (IHC), and that are, for HER2, either 0 to 1+ by IHC, or IHC 2+ and fluorescence in situ hybridization (FISH) negative (not amplified) as per current ASCO/CAP guidelines.
22. Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
23. Subject must have received a taxane or anthracycline in the neoadjuvant, adjuvant or incurable, locally advanced or metastatic setting.

   a. Prior cytotoxic regimen received in the neoadjuvant or adjuvant setting will count as a prior cytotoxic regimen if disease recurrence occurred during or within 6 months of completing the regimen.

24. Subject has progressed, relapsed, or discontinued for toxicity during or after at least 1 prior standard of care cytotoxic regimen in the incurable, unresectable locally advanced or metastatic setting, and has not received > 2 prior lines of cytotoxic therapy in the locally advanced or metastatic setting. Poly(ADP-ribose) polymerases (PARP) inhibitors do not count as a line of cytotoxic therapy.
25. Subject has received prior therapy with an anti-programmed cell death protein-1 (PD-1) or an anti-programmed cell death-ligand 1 (PD-L1) based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

<u>Cohort 3: squamous non-small cell lung cancer</u>

26. Subject has evidence of radiographic progression on or after the last regimen received.
27. Subject has histologically- or cytologically-confirmed squamous NSCLC.
    a. Subjects with mixed histology NSCLC are eligible provided there is not any component of neuroendocrine histology.
    b. Subjects with known epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), reactive oxygen species (ROS), BRAF, or other actionable mutations are eligible if treated with mutation targeted therapy and have progressed, relapsed, or discontinued treatment due to toxicity.
28. Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
29. Subject has progressed, relapsed, or discontinued treatment due to toxicity after 1 platinum-based standard of care regimen for locally advanced or metastatic disease, and has not received > 2 prior lines of cytotoxic anticancer therapy in the locally advanced or metastatic setting.
    a. Subjects with locally advanced disease who previously received curative intent treatment with platinum-based standard of care regimen in the adjuvant or neoadjuvant setting or as part of concomitant chemoradiation therapy are eligible if they have progressed or relapsed within 6 months of completion.
    b. Maintenance therapy does not constitute a new chemotherapy regimen provided there was no progression after the initial platinum-based regimen.
    c. Changing chemotherapy agents during platinum-based treatment for the management of toxicities does not constitute a new chemotherapy regimen provided no progression had occurred while on the initial therapy.
30. Subject has received prior therapy with an anti-programmed cell death protein-1 (PD-1) or anti-programmed cell death-ligand 1 (PD-L1) based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed, relapsed, or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

Cohort 4: non-squamous non-small cell lung cancer

31. Subject has evidence of radiographic progression on or after the last regimen received.
32. Subject has histologically or cytologically-confirmed non-squamous NSCLC.
    a. Subjects with mixed histology NSCLC are eligible provided there is not any component of neuroendocrine histology.
    b. Subjects with known EGFR, ALK, ROS, BRAF, or other actionable mutations are eligible if treated with mutation targeted therapy and have progressed, relapsed, or discontinued treatment due to toxicity.
33. Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
34. Subject has progressed, relapsed, or discontinued treatment due to toxicity after 1 platinum-based standard of care regimen for locally advanced or metastatic disease, and has not received > 2 prior lines of cytotoxic anticancer therapy in the locally advanced or metastatic setting.
    a. Subjects with locally advanced disease who previously received curative intent treatment with platinum-based standard of care regimen in the adjuvant or neoadjuvant setting or as part of concomitant chemoradiation therapy are eligible if they have progressed or relapsed within 6 months of completion.
    b. Maintenance therapy does not constitute a new chemotherapy regimen provided there was no progression after the initial platinum-based regimen.
    c. Changing chemotherapy agents during platinum-based treatment for the management of toxicities does not constitute a new chemotherapy regimen provided no progression has occurred while on the initial therapy.
35. Subject has received prior therapy with an anti-PD-1 or anti-PD-L1 based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed, relapsed, or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

Cohort 5: second-line or later head and neck cancer

36. Subject has evidence of radiographic progression on or after the last regimen received.
37. Subject has histologically- or cytologically-confirmed head and neck cancer.
    a. Primary tumor site must arise from the oral cavity, oropharynx, hypopharynx, and larynx; tumors arising from the nasopharynx are excluded. Salivary gland tumors and/or parotid gland tumors are not eligible for Cohort 5.
38. Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
39. Subject has progressed, relapsed, or discontinued treatment due to toxicity after 1 platinum-based standard of care regimen for locally advanced or metastatic disease, and has not received > 2 prior lines of cytotoxic anticancer therapy in the locally advanced or metastatic setting.
    a. Subjects with locally advanced disease who previously received curative intent treatment with platinum-based standard of care regimen in the adjuvant or

neoadjuvant setting or as part of concomitant chemoradiation therapy are eligible if they have progressed or relapsed within 6 months of completion.

40. Subject has received prior therapy with an anti-PD-1 or anti-PD-L1 based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed, relapsed, or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

Cohorts 6, 7 and 8: gastric or gastroesophageal junction or esophageal adenocarcinoma

41. Subject has evidence of radiographic progression on or after the last regimen received.
42. Subject has histologically- or cytologically-confirmed gastric, GEJ, or esophageal cancer.
43. Subject has locally advanced or metastatic disease that is not amenable to curative intent treatment.
44. Subject has progressed, relapsed, or discontinued due to toxicity after 1 platinum-based standard of care regimen for locally advanced or metastatic disease, and has not received > 2 prior lines of cytotoxic anticancer therapy in the locally advanced or metastatic setting.
    a. Neoadjuvant or adjuvant cytotoxic regimens will count as a prior regimen if relapsed or progressed ≤ 6 months after completion.
45. Subject must have received a HER2 directed therapy if known to have HER2 positive cancer.
46. Subject has received prior therapy with an anti-PD-1 or anti-PD-L1 based on subject's tumor PD-1 or PD-L1 expression and local treatment guidelines and has progressed, relapsed, or discontinued treatment due to toxicity, or therapy is contraindicated for subject.

Cohort 9: 1L HNSCC

47. Subject has histologically- or cytologically-confirmed head and neck squamous cell carcinoma.
    b. Primary tumor site must arise from the oral cavity, oropharynx, hypopharynx, and larynx; tumors arising from the nasopharynx are excluded. Salivary gland tumors and/or parotid gland tumors are not eligible for Cohort 9.
48. Subject has recurrent or metastatic disease that is incurable by local therapies.
49. Subject's tumor sample has PD-L1 CPS of ≥ 1 as determined by local or central IHC testing.
50. Subject has had no prior systemic therapy administered with the exception of systemic therapy completed > 6 months prior if given as part of multimodal treatment for locally advanced disease. Subjects who have received a PD-1 or PD-L1 inhibitor in the curative setting are eligible if it has been at least 12 months since last dose of the anti PD-L1 agent.
51. Subject has absolute neutrophil count (ANC) ≥ 1.5×10^9/L
52. International normalized ratio (INR) OR prothrombin time (PT) and activated partial thromboplastin (aPTT) both ≤ 1.5 × ULN unless subject is receiving anticoagulant

therapy as long as PT or aPTT is within the therapeutic range of intended use of anticoagulants. PTT may be used if local lab is unable to perform aPTT.

53. For subjects with oropharynx tumors, subject has results from testing of HPV status by p16 testing.

5.2 Exclusion Criteria

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

For all subjects:

1. Subject has preexisting sensory or motor neuropathy grade ≥ 2.
2. Subject has active central nervous system (CNS) metastases. Subjects with treated CNS metastases are permitted on study if all the following are true:
   - CNS metastases have been clinically stable for ≥ 6 weeks prior to screening
   - If requiring steroid treatment for CNS metastases, the subject is on a stable dose ≤ 20 mg/day of prednisone or equivalent for ≥ 2 weeks
   - Baseline imaging scans show no evidence of new or enlarged brain metastasis
   - Subject does not have leptomeningeal disease
3. Subject has ongoing clinically significant toxicity (grade 2 or higher with the exception of alopecia) associated with prior treatment (including systemic therapy, radiotherapy or surgery).
4. Subjects with ongoing ≥ grade 3 immunotherapy-related hypothyroidism or panhypopituitarism are excluded. Subjects with ongoing immunotherapy-related colitis, uveitis, myocarditis or pneumonitis, or subjects with other immunotherapy-related AEs requiring high doses of steroids (> 20 mg/day of prednisone or equivalent), are excluded. Subject with ≤ grade 2 immunotherapy-related hypothyroidism or panhypopituitarism may be enrolled when well-maintained/controlled on a stable dose of hormone replacement therapy (if indicated).
5. Subject has a history of uncontrolled diabetes mellitus within 3 months before the first dose of study treatment. Uncontrolled diabetes (within 3 months before first dose) is defined as hemoglobin A1c (HbA1c) ≥ 8% or HbA1c between 7 and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained. The lowest HbA1c during the screening period will be used to determine eligibility.
6. Subject has prior treatment with enfortumab vedotin or other monomethyl auristatin E (MMAE) based antibody-drug conjugates (ADCs).
7. Subject has a second malignancy diagnosed within 3 years before first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with non-melanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines)

localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.

8. Subject is currently receiving systemic antimicrobial treatment for viral, bacterial, or fungal infection at the time of first dose of study treatment. Routine antimicrobial prophylaxis is permitted.
9. Subject has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or active hepatitis C (e.g., hepatitis C virus [HCV] RNA [qualitative] is detected).
10. Subject has known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2).
11. Subject has documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction or cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III-IV within 6 months prior to the first dose of study drug.
12. Subject has major surgery within 4 weeks prior to first dose of study drug.
13. Subject had radiotherapy, chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug.
14. Subject has known hypersensitivity to enfortumab vedotin or to any excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate and polysorbate 20) OR subject has known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.
15. Subject has known active keratitis or corneal ulcerations. Subject with superficial punctate keratitis is allowed if the disorder is being adequately treated in the opinion of the investigator.
16. Subject has any condition, which, in the investigator's opinion, makes the subject unsuitable for study participation.

<u>Cohort 9: 1L HNSCC</u>

17. Had PD within 6 months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC.
18. Has had an allogeneic tissue/solid organ transplant.
19. Has severe hypersensitivity (≥ grade 3) to pembrolizumab and/or any of its excipients.
20. Has a history of (non-infectious) pneumonitis / interstitial lung disease that required steroids or has current pneumonitis / interstitial lung disease.
21. Has a history of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.

22. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (e.g., tumor bleeding, uncontrolled tumor pain) in the opinion of the treating investigator.
23. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
    a. Replacement therapy (e.g., thyroxine, insulin, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
    b. Brief (<7 days) use of systemic corticosteroids is allowed when use is considered standard of care.
    c. Subjects with vitiligo, psoriasis, type 1 diabetes mellitus, hypothyroidism, or resolved childhood asthma/atopy will not be excluded.
    d. Subjects requiring intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded.
    e. Subjects with hypothyroidism that is stable with hormone replacement or Sjögren's syndrome will not be excluded.
24. Has an active infection requiring systemic therapy.
25. Has received prior therapy with an anti-PD-1 or anti-PD-L1 agent in the recurrent/metastatic setting. If anti-PD-1 or anti-PD-L1 agent was given as part of curative intent therapy, it must be at least 1 year since last dose.
26. Has received a live vaccine within 30 days of planned start of study therapy. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
27. Subject has active tuberculosis

5.3 Restrictions During the Study

Not applicable.

5.4 Screen Failures

A screen failure is defined as a subject 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, ECG, etc.) may be repeated within the 28-day screening period without the need to register the subject as a

screen failure. If more than 28 days elapses from the date of signing the ICF, the subject must be documented as a screen failure. In order to re-screen, a new ICF must be signed and the subject entered into screening with a new subject identification number. Rescreening is only allowed once for an individual subject.

6 INVESTIGATIONAL PRODUCT(S)

6.1 Investigational Product(s) Administered

6.1.1 Enfortumab Vedotin

The investigational product, enfortumab vedotin (ASG-22CE), is a sterile, preservative-free, white to off-white lyophilized powder to be reconstituted for intravenous administration. The investigational product is supplied by Astellas in single-use glass vials containing 30 mg and/or 20 mg enfortumab vedotin in each vial. The investigational product should be stored at 2°C to 8°C.

Refer to the pharmacy manual, product label and package insert for detailed information regarding preparation, handling and storage of the enfortumab vedotin.

6.1.1.1 Dosing and Administration of Enfortumab Vedotin

Enfortumab vedotin at a dose of 1.25 mg/kg will be administered as an intravenous infusion over approximately 30 minutes on days 1, 8, and 15 of every 28-day cycle (days 1 and 8 of every 21-day cycle for cohort 9). In the absence of IRRs, the infusion rate for all subjects should be calculated in order to achieve an approximate 30-minute infusion period. Enfortumab vedotin must not be administered as an intravenous push or bolus. Enfortumab vedotin should not be mixed with other medications. At least 7 days must elapse between doses of enfortumab vedotin.

Subject weight must be measured during all relevant assessment time points as described in the Schedules of Assessments [Table 1] and [Table 2]. Weight-based dosing is calculated using the subject's actual body weight on day 1 of each cycle. **An exception to weight-based dosing is made for subjects weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose permitted on this study is 125 mg.**

Subjects should be observed during enfortumab vedotin administration and for at least 60 minutes following the infusion for the first 3 cycles. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards.

The injection site should be monitored closely for redness, swelling, pain, and infection during and at any time after administration. Subjects should be advised to report redness or discomfort promptly at the time of administration or after infusion. Events of extravasation should be managed per institutional guidelines and precautions should be taken to prevent extravasation per institutional standards.

6.1.2 Pembrolizumab (Cohort 9 Only)

Pembrolizumab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, United States Pharmacopeia (USP). Pembrolizumab will be administered as a dose of 200 mg using a 30-minute intravenous infusion on day 1 of each 3-week cycle, approximately 30 minutes after completion of the enfortumab vedotin administration. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes (-5 min/+ 10 min).

Pembrolizumab may be administered for a maximum of 35 cycles.

The pharmacy manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Packaging and Labeling

Investigational products (enfortumab vedotin [ASG-22CE] and pembrolizumab) used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at APGD-Astellas US Technologies (AUST) or sponsor's designee in accordance with APGD-AUST or sponsor's designee standard operating procedures (SOPs), 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 investigational products.

6.2.2 Handling, Storage and Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all investigational products received and any discrepancies are reported and resolved before use of investigational products.
2. Only subjects enrolled in the study may receive investigational products and only authorized study site personnel may supply or administer investigational products. Only investigational products with appropriate expiry/retest dating may be dispensed.
3. All investigational products 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.

4. 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).
5. Further guidance and instruction on final disposition of used and unused investigational product is provided in the pharmacy manual.

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

6.3 Randomization and Blinding

This is an open-label study. Subject enrollment and dispensation of investigational product will be performed via the interactive response technology (IRT) system. Prior to initiation of study treatment, study site personnel will obtain the subject number and medication assignment from the IRT system. Specific IRT procedures will be described in the respective study manual.

6.4 Investigational Product Compliance

The dose and schedule of enfortumab vedotin and pembrolizumab administered to each subject will be recorded on the eCRF for each dose. Reasons for dose delay, reduction or omission will be documented. Dosing noncompliance for enfortumab vedotin of less than or greater than 10% from each intended dose will be considered a major protocol deviation. Dosing noncompliance for pembrolizumab of 1000 mg or greater will be considered a major protocol deviation.

6.5 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

If the investigator determines that any of the following medications are necessary to provide adequate medical support to the subject, the subject must be withdrawn from further administration of the study treatment:

- Other investigational drugs
- Chemotherapy or other medications intended for antitumor activity. This does not apply to subjects on endocrine therapy, or to subjects on agents intended for the treatment of bone metastasis where subjects should be on a stable dose of bone targeting agents for at least 2 weeks prior to study entry (e.g., bisphosphonates, or receptor activator of nuclear factor kappa-B [RANK] ligand inhibitors).
- Radiation therapy except palliative radiation for nontarget lesions that is approved by the sponsor. Note: Radiation therapy to a preexisting symptomatic solitary lesion or to the bone may be considered on an exceptional case-by-case basis after consultation with the sponsor. The radiated lesion must be a nontarget lesion per RECIST Version 1.1 and the subject must have clear measurable disease outside the radiated field. Enfortumab vedotin may not be given concurrently with radiation therapy.
- Subjects who are receiving strong cytochrome P450 (CYP)3A4 inhibitors concomitantly with enfortumab vedotin should be closely monitored for adverse reactions.

- For cohort 9: Live or attenuated vaccines within 30 days prior to the first dose of study treatment and while participating in the study.
- For cohort 9: Systemic glucocorticoids except when used for the following purposes:
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - For the prevention of emesis
    - To premedicate for IV contrast allergies
    - To treat COPD exacerbations (only short-term oral or IV use in doses > 10 mg/day prednisone equivalent)
    - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
    - For topical use or ocular use
    - Intraarticular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease.

6.6 Dose Modification

6.6.1 Enfortumab Vedotin

For all cohorts, dose reduction to 1, 0.75 or 0.5 mg/kg will be allowed depending on the type and severity of toxicity. Subjects requiring a dose reduction may be re-escalated by 1 dose level (i.e., subjects reduced to 0.75 mg/kg may only be re-escalated to 1 mg/kg) provided the toxicity does not require study drug discontinuation and has returned to baseline or ≤ grade 1. If the toxicity recurs, re-escalation will not be permitted. Subjects with ≥ grade 2 corneal AEs will not be permitted to dose re-escalate.

Dose modification recommendations for enfortumab vedotin associated toxicity are presented in [Table 7] and [Table 8].

Dose interruptions for any enfortumab vedotin associated toxicities are permitted at the discretion of the investigator. Dose interruptions may last up to 8 weeks (2 cycles) for subjects in cohorts 1 to 8 and up to 6 weeks (2 cycles) for subjects in cohort 9. Dose interruptions for subjects who are deriving clinical benefit from treatment may be extended beyond 8 weeks (cohorts 1 to 8) or 6 weeks (cohort 9) after consultation with the medical monitor on a monthly basis, if the subject's toxicity does not otherwise require permanent discontinuation. During dose interruptions, disease assessments must continue to be performed at the protocol-specified frequency and disease status must remain at least SD per RECIST v1.1. If dose interruption is continuous > 6 months, the subject's study treatment will be permanently discontinued.

For all cohorts, if toxicities are present on day 1 of any cycle and enfortumab vedotin cannot be administered, then the start of the cycle may be delayed.

For cohorts 1 to 8, if toxicities are present on days 8 or 15 of any cycle and require the dose to be held > 3 days, then the dose(s) must be eliminated (skipped), rather than delayed. If a subject only receives the day 1 dose and days 8 and 15 doses need to be eliminated (skipped),

then the subject could resume the next cycle as early as day 22 (new day 1), if the toxicity has resolved by that time.

For cohort 9, if the medical monitor and site investigator determine that a dose interruption for enfortumab vedotin is needed, an interruption of all day 1 dose of pembrolizumab must also occur and may last for up to 3 weeks (1 cycle). Dose interruptions for subjects without prior dose reductions and who are responding to treatment may be dose interrupted beyond 3 weeks with approval of the medical monitor, if the subject's toxicity does not otherwise require permanent discontinuation.

If toxicities warranting a dose delay occur after day 1 dosing and are not resolved prior to day 8 dosing (up to day 10), day 8 enfortumab vedotin administration must be skipped rather than delayed. If a subject is dose-reduced due to toxicity that subsequently resolves, the subject may resume treatment at the original dose at the discretion of the medical monitor and site investigator. The day 8 dose of enfortumab vedotin must be given within 4 days of the planned dose (day 8 + 4 days). If the day 8 dose cannot be administered within this timeframe, the dose should be held until day 1 of the next treatment cycle.

Enfortumab vedotin treatment may be interrupted/delayed for other situations such as medical/surgical events or logistical reasons not related to study therapy. If such situations occur, the same dose interruption/delay instructions above will apply. If there is a dose interruption, the schedule for response assessments will not be adjusted and should still be calculated from cycle 1 day 1. The reason for interruption should be documented in the subject's study record. Participants who experience an unacceptable AE that is clearly attributable only to pembrolizumab may continue on enfortumab vedotin monotherapy until a discontinuation criterion is met.

Table 7 Recommended Dose Modifications for Enfortumab Vedotin Associated Hematologic Toxicity*

Grade 1	Grade 2	Grade 3	Grade 4
Continue at same dose level.	Continue at same dose level. For grade 2 thrombocytopenia withhold dose until toxicity is ≤ grade 1 or has returned to baseline, then resume treatment at the same dose level.	Withhold dose until toxicity is ≤ grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level. Transfusions or growth factors may be used as indicated per institutional guidelines.	Withhold dose until toxicity is ≤ grade 1 or has returned to baseline, then reduce dose by 1 dose level and resume treatment or discontinue at the discretion of the investigator. Transfusions or growth factors may be used as indicated per institutional guidelines. For anemia, treatment discontinuation should be strongly considered.
*Hematologic toxicity refers to anemia, thrombocytopenia, neutropenia and febrile neutropenia.			

Table 8 Recommended Dose Modifications for Enfortumab Vedotin Associated Non-hematologic Toxicity

Toxicity	**Grade**			
Skin reactions	Any grade			
	For suspected SJS, suspected TEN or bullous lesions, immediately withhold EV and refer the subject to a dermatologist/specialist for diagnosis and specialized care. For confirmed SJS or TEN, permanently discontinue treatment. If SJS or TEN is ruled out, see recommendations provided below for skin reactions.			
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
	Continue at same dose level. For grade 1 rash or skin reactions, the subject may continue at the same dose level. See also [Section 6.6.1.1] for recommended management of rash.	Continue at same dose level. For worsening rash or skin reactions or skin reactions with concomitant fever, withhold enfortumab vedotin until toxicity is ≤ grade 1 or has returned to baseline, and then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral of the subject to a dermatologist/ specialist for diagnosis and specialized care.	Withhold enfortumab vedotin until toxicity is ≤ grade 1 or has returned to baseline, and then resume treatment at the same dose level or consider dose reduction by 1 level. Consider referral of the subject to a dermatologist/ specialist for diagnosis and specialized care. Subjects who have confirmed SJS or recurrent ≥ grade 3 rash events should have therapy permanently discontinued.	For grade 4 AEs, discontinue treatment.[2] For confirmed SJS or TEN, or grade 4 rash or skin reactions, permanently discontinue treatment.

Toxicity	**Grade**			
Ocular	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	If ocular symptoms and/or changes in vision are identified, the subject should be evaluated with an ophthalmologic exam.[1]	Withhold dose until toxicity is ≤ grade 1 or has returned to baseline, and then resume treatment at the same dose level. For the second occurrence of grade 2 corneal AEs withhold dose until toxicity is ≤ grade 1, and then reduce the dose by 1 dose level and resume treatment. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated with an ophthalmologic exam.[1]	Discontinue treatment at the discretion of the investigator. If ocular symptoms and/or changes in vision are identified, the subject should be evaluated with an ophthalmologic exam.[1]	For grade 4 AEs, discontinue treatment.
Neuropathy	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	Continue at same dose level.	Withhold dose until toxicity is ≤ grade 1 or has returned to baseline, and then resume treatment at the same dose level. For the second occurrence of grade 2 neuropathy withhold dose until toxicity is ≤ grade 1, and then reduce the dose by 1 dose level and resume treatment.	Discontinue treatment at the discretion of the investigator.	For grade 4 AEs, discontinue treatment.

Toxicity	**Grade**			
Gastrointestinal	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is ≤ grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level.[2]	For grade 4 AEs, discontinue treatment. grade 4 vomiting and/or diarrhea that improves to ≤ grade 2 within 72 hours with supportive management does not require discontinuation.
Hyperglycemia	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	Continue at same dose level.	Continue at same dose level.	Withhold study treatment. Resume treatment once hyperglycemia/elevated blood glucose has improved to ≤ grade 2 and subject is clinically and metabolically stable.	Withhold enfortumab vedotin treatment and undertake a full evaluation of the hyperglycemia to determine the underlying diagnosis. Once blood glucose returns to ≤ grade 2, drug dosing may resume with close monitoring after consultation with the medical monitor.

Toxicity	**Grade**			
Pneumonitis/ILD	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
	Continue at same dose level.	Withhold dose until ≤ grade 1, then resume at the same dose level or consider dose reduction by 1 dose level.	Permanently discontinue treatment.	Permanently discontinue treatment.
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
All Other (not previously mentioned)	Continue at same dose level.	Continue at same dose level.	Withhold dose until toxicity is ≤ grade 1 or has returned to baseline, then resume treatment at the same dose level or consider dose reduction by 1 dose level.[3]	For grade 4 AEs, discontinue treatment.[3]

AEs: adverse events; SJS: Stevens-Johnson Syndrome; TEN: toxic epidermal necrolysis

1. Ophthalmologic exam should be performed by an ophthalmologist. In countries where optometrists can perform exams and prescribe medications, an optometrist may be used instead.
2. Grade 3/4 electrolyte imbalances/laboratory abnormalities that are not associated with clinical sequelae and/or are corrected with supplementation/appropriate management within 72 hours of their onset do not require discontinuation (e.g., grade 4 hyperuricemia).
3. Grade 3 or 4 elevations of amylase or lipase, if asymptomatic do not require treatment delay.

6.6.1.1 Enfortumab Vedotin-Related Skin Reactions (Rash and SCAR)

Low to moderate levels of Nectin-4 are also expressed on normal tissues, including skin keratinocytes, sweat glands and hair follicles; thus, skin reactions are anticipated events. As such, skin reactions are AEs of interest in all clinical studies with enfortumab vedotin.

A cumulative review of post-marketing safety data from 18 Dec 2019 (the approval date of enfortumab vedotin in the US) through 17 Dec 2022 identified reports of adverse reactions. In enfortumab vedotin monotherapy studies of urothelial carcinoma, 52.3% participants experienced at least 1 TEAE of rash and 3.8% experienced serious rash events. SAEs of rash included rash maculo-papular (1.1%), rash (0.6%), dermatitis bullous (0.5%), drug eruption (0.4%), rash vesicular (0.3%), Stevens-Johnson syndrome (SJS) (0.2%), toxic skin eruption (0.2%), and blister, eczema, erythema, erythema multiforme, rash pruritic, and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) (0.1% each).

SCAR events accounted for 22.3% of TEAEs; 1.8% of participants experienced serious SCAR, while the majority had grade 1 or 2 as the worst grade. The SAEs of SCAR included dermatitis bullous (0.5%), drug eruption (0.4%), SJS (0.2%), toxic skin eruption (0.2%), and blister, conjunctivitis, dermatitis exfoliative, erythema multiforme, stomatitis, and SDRIFE (0.1% each).

Subjects should be informed that rash and severe skin reactions have occurred after administration of EV, and to contact the Investigator immediately if they have signs and symptoms of skin reactions, oral mucosal and ocular abnormalities including mucositis or conjunctivitis. Starting in the first cycle and throughout treatment, closely monitor subjects for skin reactions. For mild to moderate skin reactions, consider appropriate treatment, such as topical corticosteroids and antihistamines as clinically indicated. For recommendations regarding dose modifications for skin reactions due to EV, refer to [Table 8].

6.6.1.2 Management of Pneumonitis/Interstitial Lung Disease related to Enfortumab Vedotin

Severe, life-threatening or fatal pneumonitis/ILD have occurred in subjects receiving enfortumab vedotin. Monitor subjects for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. For all subjects, including subjects with asymptomatic/grade 1 pneumonitis/ILD, clinical monitoring and supportive measures consistent with local medical guidelines should be followed as appropriate throughout the study. Medical intervention per standard of care should be considered for grade ≥ 2 events (e.g., corticosteroids initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). For recommendations regarding dose modifications for pneumonitis/ILD due to enfortumab vedotin, refer to [Table 8].

6.6.1.3 Management of Hyperglycemia

Investigators should monitor blood glucose levels and are advised to perform additional assessments if any symptoms of hyperglycemia are observed, including a thorough evaluation for infection. In addition, if steroids are used to treat any other condition, blood glucose levels may require additional monitoring. If elevated blood glucose levels are observed, subjects should be treated according to local standard of care and referral to endocrinology may be considered.

Subjects, especially those with a history of or ongoing diabetes mellitus or hyperglycemia, should be advised to immediately notify their physician if their glucose level becomes difficult to control or if they experience symptoms suggestive of hyperglycemia such as frequent urination, increased thirst, blurred vision, fatigue, and headache.

Subjects who enter the study with an elevated HbA1c (≥ 6.5%) at baseline should be referred to an appropriate provider during cycle 1 for glucose management. Blood glucose should be checked prior to each dosing and dose should be withheld for blood glucose > 250 mg/dL (13.9 mmol/L) (grade 3 or higher). Dosing may continue once the subject's blood glucose has improved to ≤ grade 2 and subject is clinically and metabolically stable. Blood glucose > 500 mg/dL (27.8 mmol/L) (grade 4) considered related to enfortumab vedotin requires treatment discontinuation. If a subject experiences new onset diabetes mellitus, evaluate subjects with a metabolic panel, urine ketones, HbA1c, and C-peptide to assess for new onset diabetes.

6.6.1.4 Management of Enfortumab Vedotin Infusion Related Reactions

An IRR may occur during the infusion of study treatment. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards. Supportive measures may include administering medications for IRRs.

Subjects who experience an IRR may be premedicated for subsequent infusions. Premedication may include pain medication (e.g., acetaminophen or equivalent), an antihistamine (e.g., diphenhydramine hydrochloride), and a corticosteroid administered approximately 30 to 60 minutes prior to each infusion or according to institutional standards. Should a subject experience IRRs in the setting of premedication, continued treatment with enfortumab vedotin must be discussed with the medical monitor prior to the next planned dose.

If anaphylaxis occurs, study treatment administration should be immediately and permanently discontinued.

6.6.2 Pembrolizumab

6.6.2.1 Dose Modification and Toxicity Management for Immune-mediated AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These imAEs 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. The dose of pembrolizumab should not be reduced. Based on existing clinical study data, most imAEs were reversible and could be managed with a delay of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected imAEs, 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. Based on the severity of imAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose delay and toxicity management guidelines for imAEs associated with pembrolizumab are provided in [Table 9]. Participants who experience unacceptable toxicity that is clearly attributable only to enfortumab vedotin may continue on pembrolizumab monotherapy up to a maximum of 35 cycles.

Table 9 Dose Modification and Toxicity Management Guidelines for Immune-mediated AEs Associated with Pembrolizumab

General instructions:

1. Severe and life-threatening imAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the imAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the imAE 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 imAE is ≤ grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the imAE decreased to ≤ grade 1 after corticosteroid taper.

Immune-mediated AEs	Toxicity grade (NCI-CTCAE V5.0)	Action with Pembrolizumab	imAE Management with 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 subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent grade 2, grade 3 or grade 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 subjects 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) • Subjects with grade ≥ 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Subjects 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		

Immune-mediated AEs	Toxicity grade (NCI-CTCAE V5.0)	Action with Pembrolizumab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST, 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 subjects 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	
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 subjects with T1DM • Administer antihyperglycemic in subjects with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor subjects 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 nonselective 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	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue		
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		

Immune-mediated AEs	Toxicity grade (NCI-CTCAE V5.0)	Action with Pembrolizumab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Neurological Toxicities	Grade 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		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN or DRESS	Permanently discontinue		
All Other Immune-mediated 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 4	Permanently discontinue		

AE(s): adverse event(s); ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; DRESS: Drug Rash with Eosinophilia and Systemic Symptom; GI: gastrointestinal; imAE: immune-related adverse event; IV: intravenous; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; SJS: Stevens-Johnson syndrome; T1DM: type 1 diabetes mellitus; TEN: toxic epidermal necrolysis; ULN: upper limit of normal.

Note: Non-imAE will be managed as appropriate, following clinical practice recommendations.

[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: encephalitis and other clinically important imAEs (e.g., vasculitis and sclerosing cholangitis).

6.6.2.2 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 reactions are provided in [Table 10].

Table 10 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 subject 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 hrs
	• **Stop Infusion.**
	• Additional appropriate medical therapy may include but is not limited to:
	  o IV fluids
	  o antihistamines
	  o NSAIDs
	  o acetaminophen
	  o narcotics
	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.
	• If symptoms resolve within 1 hour 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 subject should be premedicated for the next scheduled dose.
	Subjects who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.
		Subject may be premedicated 1.5 hrs (± 30 minutes) prior to infusion of study intervention with: diphenhydramine 50 mg po (or equivalent dose of antihistamine), acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

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 IV 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 subject is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Subject is permanently discontinued from further study drug treatment.	No subsequent dosing
IV: intravenous; NSAID: nonsteroidal anti-inflammatory drug; po: by mouth 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 National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 (NCI-CTCAE) at http://ctep.cancer.gov/.		

6.6.2.3 Other allowed dose interruption for pembrolizumab

If the medical monitor and site investigator determine that a dose interruption for pembrolizumab is needed, an interruption of all day 1 dose of enfortumab vedotin must also occur and may last for up to 3 weeks (1 cycle). Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study therapy. However, pembrolizumab is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the sponsor. The reason for interruption is to be documented in the subject's eCRF.

6.7 Overlapping Adverse Reactions

Some AEs, including rash or skin reactions, may represent overlapping toxicities for enfortumab vedotin and pembrolizumab, and attribution of skin reactions to an individual study treatment may be difficult. The management actions (i.e., to withhold or discontinue study treatment) for skin reactions should apply to both enfortumab vedotin and pembrolizumab, and the investigator should follow the most conservative dose modification guidelines as described in [Section 6.6]. However, for grade 2 skin reactions that are stable (not worsening and in the absence of fever) with supportive measures and not limiting the subject's activities of daily living, continued dosing of enfortumab vedotin may be considered following consultation with the sponsor.

6.8 Criteria for Continuation of Treatment

Options to provide enfortumab vedotin and/or pembrolizumab to subjects who are continuing to receive treatment and are benefiting will be determined at the time of cohort closure or study closure. The continued access to pembrolizumab will end when a criterion for discontinuation is met or 35 doses of pembrolizumab have been administered.

6.9 Treatment of Overdose

In the event of an overdose of > 10% of enfortumab vedotin, the site should notify the sponsor as soon as they are aware of the overdose. The subject should be closely monitored for adverse reactions. Supportive care per institutional standards should be administered.

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

7 STUDY PROCEDURES AND ASSESSMENTS

7.1 Efficacy Assessments

Radiographic and response assessments will be performed according to the Schedules of Assessments [Table 1] and [Table 2]. For all cohorts, disease response and progression will be evaluated using RECIST Version 1.1 (see [Appendix 12.9, RECIST Version 1.1]). In addition, for cohort 9, disease assessments will also be evaluated using iRECIST (see Section 7.1.3).

7.1.1 Imaging for Disease Assessment (Computed Tomography/Magnetic Resonance Imaging)

For cohorts 1 to 8, imaging/disease assessment will be performed at screening/baseline and every 8 weeks (56 days ± 7 days) from the first dose of study treatment throughout the study until the subject has radiologically-confirmed disease progression, initiates a new subsequent anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first. Baseline imaging performed prior to informed consent as standard of care may be used as long as it is performed within 28 days prior to the first dose of study treatment.

Disease response and progression will be assessed by the investigator. If disease response is assessed as CR or PR by investigator, a confirmatory imaging scan is required 4 weeks (28 days + 7 days) after the first response. After 1 year on study treatment, the frequency of disease response assessments will be reduced to every 12 weeks (84 days ± 7 days).

In cohort 9, the first on-study imaging/disease assessment will be performed 9 weeks (63 days ±7 days) from the first dose of study treatment and then every 6 weeks (42 days ± 7 days) throughout the study. After 18 months on study treatment, the frequency of disease response assessments will be reduced to every 9 weeks (± 7 days). Baseline imaging performed prior to informed consent as part of standard of care may be used as long as it is

performed within 28 days prior to the first dose of study treatment. Tumor imaging should also be performed whenever disease progression is suspected. Objective responses will be confirmed per RECIST Version 1.1 with repeat scans at least 4 weeks (+7 days) after first documentation of response.

Imaging for cohort 9 should include the head, neck, chest and abdomen at the specified timepoints. A CT from the vertex of the head to the thoracic inlet or a brain CT is strongly preferred. Imaging of the pelvis is optional.

Treatment beyond disease progression per RECIST Version 1.1 may be considered for subjects in cohort 9 who are deriving clinical benefit. Subjects with unconfirmed progressive disease (iUPD) who are clinically stable may continue on study treatment until iCPD per iRECIST guidelines [Seymour et al, 2017] as assessed by the investigator. Confirmatory scans should be performed at the next scheduled disease assessment (6 weeks ± 1 week).

Subjects in cohorts 1 to 8 who discontinue study treatment for reasons other than radiologically-confirmed disease progression by RECIST Version 1.1 will continue to receive imaging scans every 8 weeks (56 days ± 7 days) until subject has radiologically-confirmed disease progression, initiates a new anticancer therapy, dies, withdraws consent, lost to follow-up, or the study closes, whichever occurs first. Tumor imaging should also be performed whenever disease progression is suspected.

Subjects in cohort 9 who discontinue study treatment for reasons other than radiographically confirmed disease progression will continue to receive response assessments, including CT scans with contrast, every 6 weeks (±7 days) according to the original schedule calculated from cycle 1 day 1 up to 18 months after first dose, then every 9 weeks (±7 days). Scans are to be done until the subject has radiologically confirmed disease progression per iRECIST guidelines as determined by the investigator, initiates a subsequent anticancer therapy, dies, the study closes, or the subject withdraws consent, whichever occurs first. The investigator will make treatment decisions based on site assessments of scans by iRECIST guidelines. Clinical response will be determined at each assessment per RECIST Version 1.1 or per iRECIST guidelines when applicable. Clinical response of CR, PR, SD, or PD will be determined at each assessment.

Brain scan and bone imaging will be performed according to the Schedules of Assessments for Cohorts 1-8 in [Table 1] and brain scan according for Cohort 9 [Table 2] will be repeated at response assessment time points if metastases were identified at screening/baseline, or if metastasis is known or suspected, or as clinically indicated throughout the study.

A CT scan with contrast is the preferred modality for tumor assessment. Magnetic resonance imaging is acceptable if local standard practice or if CT scans are contraindicated in a subject (e.g., subject is allergic to contrast media). All other RECIST-approved scanning methods such as x-ray are optional. The same imaging modality should be used throughout the study. Additional instructions for imaging assessments can be found in the study procedures manual.

The assessment will include tumor measurements for target lesions, nontarget lesions and any new lesions. A response assessment will be characterized for a given time point evaluation. At the end of study for each subject, the best overall response (BOR) to the study regimen will be derived. To ensure comparability, the screening and subsequent assessment of response should be performed using identical techniques. The same individual should assess images for any 1 subject for the duration of the study if possible.

The site of disease progression including target, nontarget and/or new lesions should be documented in the eCRF. Additional imaging may be performed at any time to confirm suspected progression of disease.

This study will be analyzed based on the results of local (investigator) radiological assessments. Copies of all imaging scans will also be sent to the independent review facility in a timely manner. Images at the independent review facility will be stored. Imaging scans for a cohort may be read at the independent review facility when the minimum number of responders per investigator assessment (subjects with confirmed CR and PR) to claim promising antitumor activity at stage 1 are met based on the 2-stage BOP2 design. Central images may also be read in certain circumstances as determined by the sponsor.

7.1.2 RECIST Version 1.1 Assessment

7.1.2.1 Evaluation of Target Lesions

7.1.2.1.1 Complete Response

CR is defined as disappearance of all target and nontarget lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm from baseline measurement.

7.1.2.1.2 Partial Response

PR is defined as at least a 30% decrease in the sum of diameters (longest for nonnodal lesions; short axis for nodal lesions) of target lesions taking as reference to the baseline sum diameters.

7.1.2.1.3 Stable Disease

SD is defined as neither sufficient decrease to qualify for PR nor sufficient increase to qualify for progressive disease taking as reference the smallest sum of diameters while on study drug.

7.1.2.1.4 Progressive Disease

PD is defined as at least a 20% increase in the sum of diameters (longest for nonnodal lesions; short axis for nodal lesions) of the target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

7.1.2.2 Evaluation of Nontarget Lesions

To achieve unequivocal progression on the basis of nontarget lesions, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR of target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression.

7.1.2.2.1 Non-complete Response/Non-progressive disease

NonCR/NonPD of nontarget lesions is defined as persistence of 1 or more nontarget lesions.

7.1.2.2.2 Progressive Disease

PD of nontarget lesions is defined as unequivocal progression of existing nontarget lesions or the appearance of 1 or more new lesions.

7.1.3 iRECIST Assessment

Response will also be assessed using iRECIST guidelines [Seymour et al, 2017] for Cohort 9. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST Version 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST guidelines are designated with a prefix. iRECIST time point and best responses will be recorded separately.

Confirming Disease Progression

Unlike RECIST Version 1.1, the iRECIST guidelines require the confirmation of progression and uses the terms iUPD (unconfirmed immune progressive disease) and iCPD (confirmed immune progressive disease). Confirmatory scans should be performed at the next scheduled disease assessment (6 weeks ± 1 week). iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by 1 or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST Version 1.1 definitions of progression had been met (from nadir) in target, nontarget disease or new lesions
- Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
- Continued unequivocal progression in nontarget disease with an increase in tumor burden
- Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions
- RECIST Version 1.1 criteria are met in lesions types (target and/or nontarget and/or new lesions) where progression was not previously identified, including the appearance of additional new lesions

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD [immune stable disease], iPR [immune partial response] or iCR [immune complete response] if those criteria are met compared to baseline). Please refer to the iRECIST guidelines [Seymour et al, 2017] for more details.

New Lesions

New lesions should be assessed and measured as they appear using RECIST Version 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and nontarget lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected separately in the case report form.

7.1.4 Evaluation of Time Point Response

The response status at each time point for all subjects will be reported.

7.1.5 Survival Status

After radiologically-confirmed disease progression or initiation of subsequent anticancer therapy, whichever occurs first, subjects will be contacted every 12 weeks in the long-term follow-up period for survival status until death, withdrawal of consent, lost to follow-up, or study closure, whichever occurs first. Sponsor may choose to discontinue the collection of survival status for any cohort.

7.2 Safety Assessments

7.2.1 Adverse Events

See [Section 7.3, Adverse Events and Other Safety Aspects**]** for information regarding AE collection and data handling.

7.2.2 Laboratory Assessments

See [Appendix 12.7 Laboratory Assessments] for the list of clinical laboratory tests (including hematology, biochemistry, HbA1c and lipid panel) to be performed and refer to Schedules of Assessments [Table 1] and [Table 2] for timing and frequency. Laboratory tests will be sent to the local laboratory for analysis. Redacted copies of laboratory reports for all local laboratory testing will be submitted electronically by the site to a central vendor for data entry processing. Clinical laboratory tests will be performed locally prior to dosing. Tests will be obtained as indicated in the Schedules of Assessments [Table 1] and [Table 2]. If tests were performed within 7 days prior to the first day of dosing, they do not need to be repeated on cycle 1 day 1. Clinical laboratory tests at screening and on cycle 1 day 8 are to be performed after the subject has been fasting in order to ensure accurate interpretation of

lab test values such as glucose values. Subject will be provided with food after fasting blood samples are obtained. Fasting status will be recorded in source documents. Fasting is not necessary for laboratory tests performed at all other visits. HbA1c will be obtained at screening/baseline and EOT visits. If HbA1c is elevated (≥ 6.5%), refer subject to appropriate provider during cycle 1 for glucose management. Lipid panel, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride tests, will be obtained at screening/baseline only.

Additional assessments may be done to monitor AEs or as required by dose modification requirements. Additional laboratory tests should be performed according to institutional standard of care.

For women of childbearing potential, a serum pregnancy test will be performed at baseline. A urine or serum pregnancy test will then be repeated on day 1 of each cycle prior to study drug administration at EOT and follow-up visits. After EOT, a monthly (±7 days) pregnancy test will be maintained until 6 months after the last dose of study treatment.

The investigator or subinvestigator must review the laboratory report and document this review. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator or subinvestigator who is a qualified physician.

7.2.3 Vital Signs

Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats/minute) and temperature will be obtained as indicated in the Schedules of Assessments [Table 1] and [Table 2]. All vital sign measures will be taken prior to dosing with the subject in the sitting or supine position.

If clinically significant vital sign changes from screening/baseline are noted, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance will be defined as a variation in vital signs that has medical relevance as deemed by the investigator that could result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to grade ≤ 1, or to the baseline (pretreatment) value, or until the investigator determines that follow-up is no longer medically necessary.

7.2.4 Physical Examination

Standard, full physical examinations will be obtained as indicated in the Schedules of Assessments [Table 1] and [Table 2] to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status and lymphatic systems. Height measurement is only required at screening/baseline. Weight measurement will also be performed as indicated in the Schedules of Assessments [Table 1] and [Table 2]. If physical examination was performed within 7 days prior to the first day of dosing, it does not need to be repeated on cycle 1 day 1.

If clinically significant worsening of findings from baseline is noted at any study visit, the changes will be documented as AEs on the AE eCRF. Clinical significance is defined as any variation in physical findings that has medical relevance that could result in an alteration in

medical care. The investigator will continue to monitor the subject until the parameter returns to grade ≤ 1, or to the baseline condition, or until the investigator determines that follow-up is no longer medically necessary.

7.2.5 Electrocardiogram

Routine 12-lead ECGs will be performed and assessed using local standard procedures as indicated in the Schedules of Assessments [Table 1] and [Table 2]. If clinically significant worsening of a finding from baseline is noted, the abnormality will be documented as AEs on the AE eCRF.

Prior to performing 12-lead ECGs, subjects should rest in supine position (or semi-recumbent, if supine is not tolerated) for 10 minutes. ECGs will be read and assessed locally.

7.2.6 Complete Eye Examination

Subjects will have a complete eye examination at screening performed by a qualified ophthalmologist or optometrist who can perform exams and prescribe medications in the country. The complete eye examination includes but not limited to: visual acuity, slit lamp, tonometry examination, and dilated fundus examination. Subsequent eye examinations are to be conducted as clinically indicated. EOT slit lamp examinations are required for subjects who experience ocular AEs during the study. EOT slit lamp examinations (only required for subjects who experience ocular AEs during the study) must be performed at least 4 weeks from last dose.

7.2.7 Cohort 9 Follow-Up Assessments

Subjects who discontinue study treatment will receive physical exams, ECOG assessment, and response assessments every 6 weeks (±1 week) after EOT up to 18 months after first dose, then every 9 weeks (±1 week). Scans are to be done until radiologically confirmed disease progression on or following study treatment per iRECIST guidelines as determined by the investigator; initiation of a subsequent anticancer therapy, subject death, study closure, or withdrawal of consent, whichever occurs first. During study treatment, palliative radiotherapy on a nontarget bone lesion that is not progressing (as long as a target lesion is not within the field of radiation) will not be considered a subsequent anticancer therapy; however, radiotherapy on any target lesion will be a subsequent anticancer therapy.

7.2.8 Order of Assessments

The following order should be followed when more than 1 assessment is required at a time point with blood sampling for pharmacokinetics/biomarker profiling being collected nearest to the scheduled time point:

- ECG and/or vital signs
- Blood collection

7.3 Adverse Events and Other Safety Aspects

The definitions of an AE or SAE can be found in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up or Reporting].

The investigator and medically qualified designee(s) are responsible for detecting, documenting and recording events that met the definition of an AE or SAE.

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

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received investigational product. AE and ECI collection begins after the signing of the ICF and will be collected until 30 days after the last dose of investigational product administration or when the subject is determined to be a screen failure. SAEs related to pembrolizumab will be collected until 90 days after following cessation of study treatment, or 30 days following cessation of study treatment if the subject initiates new anticancer therapy, whichever is earlier.

7.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The methods of recording, evaluating and assessing seriousness, causality and severity of AEs and SAEs are described in [Appendix 12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up or Reporting]. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

An AE with a change in severity is recorded as a new AE.

7.3.3 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

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 (serious adverse event or adverse event) including death, where he/she considers there is reasonable possibility it is related to the investigational product or study participation, the investigator must promptly notify the sponsor.

7.3.4 Reporting of 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 subjects and the safety of a study intervention under clinical investigation are met.

In the case of an SAE, the investigator must contact the sponsor by fax or email immediately (within 24 hours of awareness).

Procedures for reporting SAEs to the sponsor are described in [Section 12.4.5 Reporting Procedures for Serious Adverse Events].

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 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 investigational product and the event, it should be reported as an (S)AE. All deaths up to 30 days after the final administration of investigational product must be reported as an SAE, even if attributed to disease progression. For subjects in Cohort 9 receiving pembrolizumab, all deaths up to 90 days after the final administration of pembrolizumab 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 preexisting condition that did not worsen during the course of the study. These procedures are collected per the eCRF's completion guidelines.

7.3.6 Events of Clinical Interest Requiring Immediate Reporting (Cohort 9 only)

For cohort 9, selected non-serious and SAEs are also known as Events of Clinical Interest (ECI) and must be collected via the SAE worksheet or an applicable form (**Unique to Japan**) and reported to the sponsor within 24 hours of awareness as described in [Section 12.4.5 Reporting Procedures for Serious Adverse Events].

ECIs for this study include:

1. An overdose of sponsor's product, as defined in [Section 6.9 Treatment of Overdose], that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT laboratory value that is ≥ 3 × ULN and an elevated TBL laboratory value that is ≥ 2 × ULN and, at the same time, an alkaline phosphatase laboratory value that is < 2 × ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.
   Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria are to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to

proceed with additional evaluation will be made through consultation between the study investigators and the sponsor Medical Expert. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

7.3.7 Special Situations

Certain special situations observed in association with the investigational product, such as incorrect administration (e.g., wrong dose of investigational product or background therapy) are collected in the eCRF, as protocol deviation per [Section 10.3 Major Protocol Deviations] 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 in the eCRF. If the AE meets the definition of an SAE, the SAE is to be reported as described in [Section 12.4.5 Reporting Procedures for Serious Adverse Events] and the details of the associated special situation are to be included in the clinical description on the SAE worksheet.

The special situations are:

- Pregnancy
- Lack of efficacy
- Medication error, overdose and use outside protocol
- Misuse/abuse
- Occupational exposure
- Suspected drug-drug interaction

Instructions and procedures for reporting special situations are provided in [Appendix 12.4.6 Reporting Procedures for Special Situations].

7.3.8 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 subjects, who will be required to sign an updated ICF in order to continue in the study.

For investigational sites located in Japan:

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 subjects, in compliance with [Appendix 12.1.4.2 Supply of New and Important Information Influencing the Subject'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.

7.3.9 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 (CA), IRB/IEC, where applicable, in order to protect subjects 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.

7.3.10 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the medical monitor/medical expert and/or Astellas study team member (within 24 hours of awareness). Full details of the potential USM are to be recorded in the subject'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 subjects. 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.

7.4 Pharmacokinetics

Blood samples (7 mL/sample) for the analysis of ADC and MMAE will be collected as indicated in the Schedules of Assessments [Table 1] and [Table 2] for the evaluation of pharmacokinetics.

Blood samples should be collected via a peripherally placed intravenous cannula or by direct venipuncture, which should always be performed on the opposite arm of the study drug infusion line. Only in the case where venous access cannot be gained from the opposite arm of the study drug infusion line, then the arm of the study drug infusion line should be used. In the event that blood cannot be drawn by venipuncture, the central line may be used. If

blood is collected from central line, use the lumen that was not used to administer the study drug.

Bioanalysis of ADC and MMAE in serum or plasma will be performed using validated methods at bioanalytical laboratories specified by the sponsor.

The actual date and time of each blood sample collection will be documented. Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a Sponsor designated analytical laboratory.

When deemed appropriate, plasma samples remaining after the pharmacokinetic analysis may be used for exploratory metabolic profiling or exploratory biomarker analysis after the study. These tests will be described in a separate report and will not be incorporated in the integrated clinical study report (CSR).

7.5 Pharmacodynamics | Immunogenicity

Blood samples will be collected during the study treatment period, at EOT and safety follow-up visits for determination of ATA concentrations. Blood samples (4 mL/sample) will be collected at the time points indicated in the Schedules of Assessments ([Table 1] for cohorts 1 to 8 and [Table 2] for cohort 9).

Blood samples should be collected via a peripherally placed intravenous cannula or by direct venipuncture, which should always be performed on the opposite arm of the study drug infusion line. Only in the case where venous access cannot be gained from the opposite arm of the study drug infusion line, then the arm of the study drug infusion line should be used. In the event that blood cannot be drawn by venipuncture, the central line may be used. If blood is collected from central line, use the lumen that was not used to administer the study drug.

Bioanalysis of ATA in serum will be performed using validated methods at bioanalytical laboratories specified by the sponsor.

Blood sampling, processing, storage and shipment instructions will be provided in the laboratory manual. Samples will be shipped to and analyzed by a sponsor designated analytical laboratory.

7.6 Other Assessments

7.6.1 Banked Pharmacogenomic Sample (Optional)

PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety. 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 banking contract research organization (CRO).

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

See [Appendix 12.8 Pharmacogenomic Analysis with Banked Sample] for further details on the banking procedures.

7.6.2 Exploratory Biomarker(s)

The procedures for the collection, handling and shipping of laboratory samples submitted to the central laboratory will be specified in a laboratory manual.

The samples described in [Section 7.6.2.1 Blood Sample for Biomarker Analysis, Section 7.6.2.2 Tumor Tissue Samples for Biomarker Analysis, and Section 7.5 Pharmacodynamics/Immunogenicity] 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 enfortumab vedotin.

The samples will be stored at the study sponsor's facility or a contract laboratory facility for up to 15 years after study database hard-lock, at which time the samples will be destroyed.

7.6.2.1 Blood Sample for Biomarker Analysis

Blood samples for biomarker analysis will be collected from all subjects at the time points indicated in the Sample Collection Schedule [Table 3 and Table 4] for the isolation of plasma, serum, and peripheral blood mononuclear cells (PBMCs). A subset of the plasma samples may be used for the next-generation sequencing (NGS) analysis of circulating free DNA (cfDNA). A subset of the serum samples may be used to characterize soluble Nectin-4 levels. The plasma, serum, and PBMC samples may undergo cytokine or immune-phenotyping analysis to identify markers of immune function and immune cell subsets. The blood samples may be used for additional exploratory analyses as described in [Section 7.6.2 Exploratory Biomarker(s)].

7.6.2.2 Tumor Tissue Samples for Biomarker Analysis

For all cohorts, pretreatment tumor tissue sample (from primary or metastatic site) in the form of a formalin-fixed, paraffin-embedded tumor tissue block or unstained charged slides as indicated in the Schedules of Assessments [Table 1] and [Table 2] is required for submission to the sponsor (unless prior approval is obtained from the sponsor). Either archival or pretreatment fresh tumor tissue is acceptable. If an archival tumor tissue sample is not available, the subject will have a biopsy to obtain tumor tissue prior to study treatment. If freshly sectioned, unstained charged slides are submitted, a minimum of 10 and up to 20 slides are needed from each subject for the planned biomarker studies. If at least 10 slides cannot be sectioned from available block, site will be required to provide as many as possible and discuss with the sponsor. If multiple blocks will be used to produce slides, site should contact the sponsor before cutting the blocks. See the laboratory manual for details, including FFPE stability requirements.

For cohort 9, the pretreatment tumor tissue will be sent for central testing using the Agilent PD-L1 IHC 22C3 pharmDx assay to evaluate PD-L1 status. A PD-L1 CPS ≥ 1 is required for enrollment in cohort 9. A local test result may be used for eligibility.

If biopsy is performed as standard of care while on study treatment or during follow-up period, subject's tumor tissue samples are requested to be submitted to sponsor, if available.

The tumor tissue samples may be analyzed for Nectin-4 and PD-L1 expression, markers of disease subtype and markers related to the tumor immune microenvironment. The tumor tissue sample may be used for additional exploratory analyses as described in [Section 7.6.2 Exploratory Biomarker(s)].

For biopsies, the investigator, in consultation with other specialists, as needed (e.g., radiology staff) will assess the risk associated with obtaining a tumor tissue sample and determine if the subject is an appropriate candidate for the procedure. Biopsies should be obtained in accordance with institutional policies/guidelines to minimize risk. Procedures requiring general anesthesia should not be performed to obtain a tumor tissue sample; however, if a surgical procedure under general anesthesia is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

7.6.3 Quality of Life and Patient Reported Outcome Assessment

Quality of life (QOL) questionnaires will be assessed using EQ-5D-5L and pain assessment rating scale at the time point as indicated in the Schedules of Assessments [Table 1] and [Table 2]. The PRO data will be completed on paper forms by the subject and should always be completed first at every schedule clinic visit prior to dosing and any other study assessments, especially discussion of disease status. Subjects who do not speak a language for which translated QOL questionnaires are available or who is illiterate and therefore will not be able to complete the QOL questionnaires may be enrolled into the study and exempted from completing QOL questionnaires after consultation with the sponsor.

7.6.3.1 Cohorts 1 to 8:

7.6.3.1.1 Global Pain Assessment

The subject will rate his/her pain on a 0 to 10 scale that best describes the pain at its worst in the last 24 hours. See [Appendix 12.11 Pain Assessment].

7.6.3.1.2 Euro Quality of Life-5 Dimensions

The EQ-5D-5L is a standardized instrument developed by the EuroQOL Group for use as a generic, preference-based measure of health outcomes. It is applicable to a wide range of health conditions and treatments and provides a simple descriptive profile and a single index value for health status. The EQ-5D-5L is a 5-item self-reported measure of functioning and well-being, which assesses 5 dimensions of health, including mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems). A unique EQ-5D-5L health state is defined by combining 1 level from each of the 5 dimensions. This questionnaire also records the respondent's self-rated health status on a

vertical graduated (0 to 100) visual analogue scale [Herdman et al, 2011]. See [Appendix 12.12 EQ-5D-5L].

7.6.3.2 Cohort 9

7.6.3.2.1 EORTC QLQ H&N43

The EORTC H&N43 contains 43 items of 6 multi-item and 13 single-item symptom subscales namely pain, swallowing, senses problems, speech problems, trouble with social eating, less sexuality, teeth, dry mouth/sticky saliva, body image, shoulder pain, skin problems, anxiety, trouble with social contact, opening mouth, coughing, lymphedema, problems wound healing, weight loss, neurological problems.

7.6.3.2.2 Global Pain Assessment

The subject will rate his/her pain on a 0 to 10 scale that best describes the pain at its worst in the last 24 hours. See [Appendix 12.11 Pain Assessment].

7.6.3.2.3 PRO-CTCAE

Three questions will be utilized from the PRO-CTCAE to obtain subject assessment of fatigue and diarrhea symptoms.

7.6.3.3 FACT-G

Functional Assessment of Cancer Therapy – General (FACT-G) Version 4 is a 27-item questionnaire designed to measure four domains of HRQOL in cancer patients: Physical, social, emotional, and functional well-being. Original development and validation involved 854 patients with cancer and 15 oncology specialists. Subjects with cancer aged 18 years and older are asked to recall the past 7 days and complete the questionnaire. EV-202 cohort 9 will include a single question from the “Physical Well-Being” domain, GP5 “I am bothered by side effects of treatment” which is self-scored from “0 to 4” (0 - not at all; 1 - A little bit; 2 - Somewhat; 3 - Quite a bit; 4 - very much).

7.7 Total Amount of Blood

The total amount of blood for each subject will vary depending on the course of their disease, duration on treatment and local laboratory requirements. At any time during the study, if any laboratory abnormalities are found for a subject, additional blood may be drawn for safety monitoring.

For cohorts 1 to 8, the maximum amount of blood collected is approximately 52 mL on cycle 1 day 1, 41 mL on cycle 1 day 8, and 48 mL on cycle 1 day 15. The maximum amount of blood collected for subjects that participate from cycle 2 up to cycle 6 and completes the EOT visit is approximately 185 mL.

For cohort 9, the maximum amount of blood collected is approximately 52 mL on cycle 1 day 1, 41 mL on cycle 1 day 8, and 8 mL on cycle 1 day 15. The maximum amount of blood collected for subjects that participate from cycle 2 up to cycle 6 and completes the EOT visit is approximately 233 mL.

8 DISCONTINUATION

8.1 Discontinuation of Individual Subject(s) From Study Treatment

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

The subject 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 subject from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

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

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

- Subject develops documented radiological disease progression (iCPD per iRECIST) in cohort 9).
- Subject starts a new anticancer therapy.
- Subject develops unacceptable toxicity.
- Female subject becomes pregnant.
- Investigator decides it is in the subject's best interest to discontinue.
- Subject requests to stop treatment.
- Subject is noncompliant with the protocol based on the investigator or medical monitor assessment.
- Subject has continuous dose interruption > 6 months.
- Study is terminated by sponsor.

For subjects in cohort 9, Pembrolizumab may be administered for up to a total of 35 cycles (approximately 2 years). Subjects who experience an unacceptable AE that is clearly attributable only to pembrolizumab may continue on enfortumab vedotin monotherapy until a discontinuation criterion is met. Subjects who experience unacceptable toxicity that is clearly attributable only to enfortumab vedotin may continue on pembrolizumab monotherapy up to a maximum of 35 cycles.

8.2 Discontinuation of Individual Subject(s) From Study

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol-specific follow-up procedures as outlined in the Schedules of Assessments [Table 1] and [Table 2]. The only exception to this is when the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. A subject may be discontinued from the study for any of the following reasons:

- Lost to follow-up
- Death
- Subject withdrawal of consent
- Study termination by sponsor

8.2.1 Lost to Follow-up

Every reasonable effort is to be made to contact any subject lost to follow-up during the course of the study to complete study-related assessments and record outstanding data.

8.3 Discontinuation of the Study Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor and, if applicable, the head of the study site.

8.4 Discontinuation of the Study

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

9 STATISTICAL METHODOLOGY

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. The SAP will be finalized before the database hard-lock at the latest. Changes from the planned analyses in the final SAP that impact the statistical analyses will be justified in the clinical study report (CSR).

In general, data will be summarized by cohort and overall with descriptive statistics for continuous endpoints, and frequency and percentage for categorical endpoints. Kaplan-Meier estimates will be provided for time-to-event endpoints.

9.1 Sample Size

The planned sample size for cohorts 1 to 8 is 40 subjects in each cohort. Assuming the reference ORR for the 7 tumor types chosen for the study, ranges from 10% to 20%, and at least a 10% absolute increase in ORR is considered clinical meaningful improvement, the sample size of 40 subjects allows an 80% confidence interval of enfortumab vedotin ORR to exclude the reference ORR. The actual sample size for each cohort may be less than the planned sample size depending on the ORR analysis result at the planned interim analysis. Per Bayesian optimal design for phase 2 (BOP2), the enrollment of a cohort maybe stopped after interim analysis.

The planned sample size for cohort 9 is 40 subjects. Assuming the reference ORR for cohort 9 is 20%, and at least a 25% absolute increase in ORR is considered clinical meaningful improvement for combination therapy, the sample size of 40 subjects allows a 92% power to detect a statistically significant difference at type 1 error rate of 1-sided 0.025. The actual sample size for cohort 9 may be less than the planned sample size depending on the ORR analysis result at the planned interim analysis. Per Bayesian optimal design for phase 2 (BOP2), the enrollment of a cohort maybe stopped after interim analysis.

9.2 Analysis Sets

The allocation of subjects to analysis sets will be determined prior to database hard-lock.

9.2.1 Full Analysis Set

The full analysis set (FAS) consists of all enrolled subjects who receive any amount of study drug. The FAS is used for primary analysis on OS and PFS.

9.2.2 Response Evaluable Set

The response evaluable set (RES) is a subset of the FAS. It consists of the FAS subjects who have measurable disease at baseline per investigator assessment and have at least 2 postbaseline scans or no longer in the follow-up of response at the time of analysis. The RES is the primary analysis set for the response related efficacy analysis.

9.2.3 Safety Analysis Set

The safety analysis set (SAF) consists of all subjects who receive at least 1 dose of study drug. The SAF will be used for all summaries of the safety data.

9.2.4 Pharmacokinetic Analysis Set

The pharmacokinetics analysis set (PKAS) consists of subjects who receive at least 1 dose of study drug and for whom at least 1 blood sample is collected and assayed for measurement of enfortumab vedotin and MMAE serum/plasma concentrations and for whom the time of sampling and the time of dosing on the day of sampling is known.

9.3 Demographics and Baseline Characteristics

9.3.1 Demographics

Demographics and baseline characteristics will be summarized by cohort and overall for all treated subjects. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

9.3.2 Subject Disposition

The number and percentage of subjects who discontinued treatment and reasons for treatment discontinuation will be presented for subjects in the SAF by cohort and overall. Similar tables for screening disposition and follow-up disposition will also be presented.

9.3.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

All previous and concomitant treatment will be listed. The frequency of concomitant treatment will be summarized by cohort and overall.

9.3.4 Medical History

Medical history for each subject will be listed.

9.3.5 Investigational Product Exposure

The number and percentage of subjects exposed to study drug will be summarized by cohort.

All study drug exposure data will be listed.

9.4 Analysis of Efficacy

Efficacy analysis will be conducted on the RES and FAS as specified in [Section 9.2 Analysis Sets]. For cohorts 1 to 8, tumor related analyses will be summarized based on RECIST Version 1.1. For cohort 9, tumor related analyses will be summarized based on RECIST Version 1.1 and iRECIST.

9.4.1 Analysis of Primary Endpoint

9.4.1.1 Primary Analysis

The primary efficacy endpoint is the confirmed ORR per investigator assessment. Confirmed ORR is defined as the proportion of subjects whose BOR is a confirmed CR or PR according to RECIST Version 1.1. The confirmed ORR for each cohort will be calculated and its 95% confidence interval will be constructed by the Clopper-Pearson method. The primary analysis set for confirmed ORR is RES. Additionally, confirmed ORR by Nectin-4 expression analysis may be conducted.

9.4.2 Analysis of Secondary Endpoints

9.4.2.1 Duration of Response

DOR is defined as the time from the date of first documented response (CR or PR that is subsequently confirmed) to the date of first documented PD per RECIST Version 1.1 or death due to any cause, whichever occurs first. DOR will only be calculated for subjects achieving a confirmed CR or PR. DOR will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median DOR and its 2-sided 95% CI will be calculated.

9.4.2.2 Disease Control Rate

DCR is defined as the proportion of subjects whose BOR is confirmed CR or PR or SD per RECIST Version 1.1. DCR for each cohort will be calculated and its 95% confidence interval will be constructed by Clopper-Pearson method.

9.4.2.3 Progression-free Survival

PFS is defined as the time from start of study treatment to first documentation of PD per RECIST Version 1.1 or death due to any cause, whichever comes first. PFS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS and its 2-sided 95% CI will be calculated.

9.4.2.4 Overall Survival

OS is defined as the time from start of study treatment to date of death due to any cause. OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its 2-sided 95% CI will be calculated.

9.4.3 Analysis of Other Efficacy Endpoints

9.4.3.1 Best Overall Response

BOR will be determined based on all available tumor time point response data for the subject. Responses recorded after new anticancer therapy or progressive disease (PD), will be excluded from BOR derivation. A frequency table of BOR will be presented for each cohort and overall.

The BOR will be derived according to below criteria per RECIST Version 1.1:

- If a subject has at least 2 CR and the first and the last CR dates are more than 28 days apart, then the BOR is defined as confirmed CR.
- If a subject has PR and another CR/PR more than 28 days apart, then the BOR for this subject is confirmed PR.
- For those subjects who do not have confirmed CR or PR, if the subject has at least 1 tumor assessment record of CR/PR/SD which is at least 49 days after the date of the first dose, then BOR is defined as SD.
- For subjects who do not have confirmed CR, confirmed PR or SD defined as above, but they have the last tumor assessment as PD, their BOR is PD.
- Otherwise, BOR is defined as Not Evaluable (NE) or No Data (ND) for the subjects without any post-baseline tumor assessment data.

9.4.3.2 Sum of Diameters

Per RECIST Version 1.1, tumor burden is measured by the sum of diameters (SOD) of all target lesions at each tumor assessment. The maximum percent reduction from baseline in SOD will be calculated for each subject and presented graphically with a waterfall plot.

9.4.3.3 Time to Response

Time to response (TTR) will be calculated as the time from the first dose of study drug to the first documentation of objective response (CR or PR that is subsequently confirmed) per RECIST Version 1.1. TTR will only be calculated for subjects achieving a confirmed CR or PR. TTR will be summarized by descriptive statistics.

9.4.3.4 iRECIST Efficacy Endpoints

For Cohort 9, separate endpoints of iORR, iDCR, iDOR, and iPFS will be analyzed based on iRECIST guidelines.

Confirmed iORR is defined as the proportion of subjects whose BOR is a confirmed iCR or iPR according to iRECIST as assessed by investigator. The confirmed iORR for cohort 9 will be calculated and its 95% confidence interval will be constructed by the Clopper-Pearson method. The analysis set for confirmed iORR is RES.

iDCR with confirmed response is defined as the proportion of subjects whose BOR is confirmed iCR or confirmed iPR or iSD per iRECIST as assessed by investigator. iDCR for cohort 9 will be calculated and its 95% confidence interval will be constructed by Clopper-Pearson method.

iDOR is defined as the time from the date of first documented response (iCR or iPR whichever is first recorded) to the date of first documented radiological disease progression per iRECIST as assessed by investigator or death due to any cause, whichever occurs first. iDOR will only be calculated for subjects achieving a confirmed iCR or iPR. iDOR will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median iDOR and its 2-sided 95% CI will be calculated.

iPFS is defined as the time from start of study treatment to first documentation of radiological disease progression per iRECIST as assessed by investigator or death due to any cause, whichever comes first. iPFS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median iPFS and its 2-sided 95% CI will be calculated.

9.4.4 Analysis of the Central Imaging Data

Imaging scans for a cohort may be read at the independent review facility when the minimum number of responders per investigator assessment (subjects with confirmed CR and PR) to claim promising antitumor activity at stage 1 are met based on the 2-stage BOP2 design. Central images may also be read in certain circumstances as determined by the sponsor.

Confirmed ORR, DOR, DCR, and PFS will be analyzed for the cohort with response assessment evaluated by BICR. These endpoints will be analyzed similarly as the corresponding endpoint per investigator assessment except that subjects are required to have measurable disease at baseline per BICR.

9.5 Analysis of Safety

9.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

A TEAE is defined as an AE observed after starting administration of study drug and within 30 days after the final administration of study drug. A drug-related TEAE is defined as any TEAE with a causal relationship assessed as “yes” by the investigator.

The number and percentage of subjects 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 system organ class (SOC), preferred term, cohort, and overall. 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 subject.

AE data will be listed.

9.5.2 Laboratory Assessments

For quantitative clinical laboratory measurements, observed value and changes from baseline will be summarized with descriptive statistics at each visit.

Shift from baseline to worst post-baseline National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI-CTCAE) grade will be summarized for each the selected lab parameters.

Laboratory data will be listed.

9.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by cohort and overall at each visit.

Vital signs data will be listed.

9.5.4 Physical Examination

Physical examinations will be listed.

9.5.5 Electrocardiogram

9.5.5.1 Routine 12-lead Electrocardiogram

The routine 12-lead ECG results will be summarized by cohort and overall at each visit.

9.5.6 Eastern Cooperative Oncology Group (ECOG) Performance Scores

Number and percent of subjects for each category of the ECOG performance status at each assessment time will be provided. Grades range from 0 (fully active) to 5 (dead). Negative change in scores indicates an improvement and positive change in scores indicates a decline in performance. ECOG will also be summarized using shift table from baseline to maximum post-baseline.

9.6 Analysis of Pharmacokinetics

Concentrations of enfortumab vedotin and MMAE will be summarized using descriptive statistics (n, mean, SD, coefficient of variation [CV], geometric mean, geometric CV, median, minimum and maximum) at each pharmacokinetic sampling time point for the PKAS. Additional model-based analyses and exposure response may be performed and reported separately.

9.7 Analysis of Pharmacodynamics | Immunogenicity

The number and percentage of subjects with positive ATA for enfortumab vedotin will be presented. In addition, for subjects with positive antibodies, individual subject titer levels will be displayed at each visit in a listing.

9.8 Analyses of Exploratory Biomarker(s)

Associations between potential genomic and/or other biomarkers (including Nectin-4 expression), and clinical results (efficacy, safety or pharmacodynamics) may be performed on

subjects 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.

9.9 Analysis of Quality of Life and Patient Reported Outcome Parameters

Descriptive QOL and PRO analyses will be performed. Completion rate for each questionnaire will be summarized. Additional analyses will be discussed in detail in the SAP.

9.10 Major Protocol Deviations

Major protocol deviations as defined in [Section 10.3 Major Protocol Deviations] will be summarized for all enrolled subjects by cohort and overall, as well as by study site.

Major protocol deviation data will be listed by study site and subject.

The major protocol deviation criteria will be uniquely identified in the summary table and listing.

9.11 Interim Analysis (and Early Discontinuation of the Study)

For each cohort, one planned interim analysis will be performed to evaluate confirmed ORR at the time when 20 subjects had evaluable tumor response data per investigator assessment following study treatment. The interim analysis decision rule is based on Bayesian optimal phase 2 (BOP2) design [Zhou et al, 2017].

Specifically, let n denote the interim sample size and N denote the maximum sample size. For cohort i, let p_{0i} denote the reference ORR, p_{1i} denote the target ORR and $p_{eff,i}$ denote the treatment ORR of cohort i, and define the null hypothesis $H_{0i}: p_{eff,i} \leq p_{0i}$, representing that the treatment is inefficacious. At the time of the interim analysis for each cohort, the sponsor will stop enrolling subjects and claim that the treatment is not promising if

$$Prob(p_{eff,i} > p_{0i}|data) < \lambda(\frac{n}{N})^{\alpha},$$

where λ and α are design parameters optimized to minimize the chance of incorrectly claiming that an efficacious treatment is not promising (i.e., type II error) under the alternative hypothesis $H_{1i}: p_{eff,i} = p_{1i}$, while controlling the type I error rate at 0.1 (i.e., the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 10%) for cohorts 1 to 8 and 0.025 for cohort 9. For this study, $\alpha = 1$ is selected for all 9 cohorts to have reasonable probability of early stopping, grid search was performed to identify an optimal λ for each cohort depending on their corresponding reference ORR (i.e., p_{0i}) and target ORR (i.e. p_{1i}). Optimal λ for each cohort are included in [Table 11]. Assuming a Beta(p_{0i}, $1 - p_{0i}$) prior distribution for $p_{eff,i}$, the above decision rules are corresponding to the following stopping boundaries:

Table 11 Optimal λ for Each Cohort

Cohort (Reference ORR vs. Target ORR) λ, α	Interim Analysis (Stage 1)		Final Analysis (Stage 2)	
	Number of Evaluable Subjects	Minimum number of Responders to Proceed to Stage 2	Number of Evaluable Subjects	Minimum number of Responders to Claim Promising Antitumor Activity
Cohort 1 ($p_{0i} = 0.2$ vs. $p_{1i} = 0.3$) $\lambda = 0.91, \alpha = 1$	20	4	40	12
Cohort 2/4 ($p_{0i} = 0.15$ vs. $p_{1i} = 0.25$) $\lambda = 0.885, \alpha = 1$	20	3	40	10
Cohort 3/5/6†/7/8 ($p_{0i} = 0.1$ vs. $p_{1i} = 0.2$) $\lambda = 0.84, \alpha = 1$	20	2	40	7
Cohort 9 ($p_{0i} = 0.2$ vs. $p_{1i} = 0.45$) $\lambda = 0.98, \alpha = 1$	20	5	40	14

†Interim analysis for Cohort 6 will be conducted when applicable under protocol versions 1.0 and 2.0 based on enrollment status. Subjects initially enrolled in Cohort 6 will be reallocated to Cohort 7 or 8 based on tumor type/histology.

Based on the above table, using cohort 1 as an example, the sponsor will perform the interim analysis when the number of evaluable subjects with HR+/HER2- breast cancer reaches 20. If the total number of responders among the 20 evaluable subjects is less than 4, the enrollment of cohort 1 may stop; otherwise the enrollment will continue until the total number of evaluable subjects reaches the maximum sample size of 40. The sponsor will make the final decision on stopping cohort enrollment based on the overall evaluation of antitumor activity and safety data including subject's Nectin-4 expression data. At the final analysis, taking into account overall antitumor activity (including central imaging data) and safety data, the sponsor will conclude that the treatment is promising if the number of responders among 40 are greater or equal to 12; otherwise the sponsor will conclude that the treatment is not promising.

9.12 Additional Conventions

Imputation methods for missing data, if applicable, and the definitions for windows to be used for analyses will be outlined in the SAP.

10 OPERATIONAL CONSIDERATIONS

10.1 Data Collection

The investigator or site designee will enter data collected using an electronic data capture system. In the interest of collecting data in the most efficient manner, the investigator or designee should record data (including clinical laboratory values, subject questionnaire data, if applicable) in the eCRF within 5 days after the subject's visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with the source. These documents should be appropriately maintained by the study site.

The monitor should perform source data review on all critical data and processes.

Clinical laboratory tests and ECG will be performed at a local laboratory. Redacted copies of all clinical laboratory reports will be submitted to a central vendor for data entry processing. The central data entry vendor will transfer data to the sponsor at predefined intervals during the study and provide the sponsor or designee with a complete and clean copy of the data.

Subject quality of life questionnaires and PRO data as described in [Section 6.6.1.4 Management of Enfortumab Vedotin Infusion Related Reactions] will be completed on paper forms by the subject and entered into the eCRF by the site study personnel. The investigator or designee will review the questionnaire data throughout the study to ensure completion and protocol compliance.

10.2 Demographics and Baseline Characteristics

10.2.1 Demographics

Demographic information will be collected for all subjects as allowed per local regulation and will include date of birth, sex, race, ethnicity and tobacco use history (pack years).

10.2.2 Medical History

Medical history will include all significant medical conditions other than the target disease have resolved prior to informed consent or are ongoing at the time of consent. Details that will be collected include the onset date and recovery date and Common Terminology Criteria for Adverse Events (CTCAE) grade, if applicable for ongoing conditions.

10.2.3 Diagnosis of the Target Disease, Severity and Duration of Disease

For the target disease (HR+/HER2-, TNBC, Squamous NSCLC, Non-squamous NSCLC, head and neck cancer, gastric, GEJ, or esophageal cancer), the following information including but not limited to will be collected during the screening period, and be entered in the eCRF:

- Date of initial diagnosis of the primary cancer, histological type, date of histopathological or cytopathological diagnosis
- Date of diagnosis for the locally advanced or metastatic or recurrent disease
- Disease stage at screening
- Sampling method and the biopsy site of the tumor tissues (primary vs. metastatic) for Nectin-4 expression analysis

Previous treatment (including medication, radiotherapy and surgery) for underlying disease.

10.2.4 Performance Status

The ECOG Scale [Oken, 1982] will be used to assess performance status. Refer to [Appendix 12.10 Eastern Cooperative Oncology Group Performance Status].

10.3 Major Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. All deviations from the protocol are to be recorded. A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety and well-being of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to subjects.

A major protocol deviation is one that may potentially impact the completeness, accuracy or reliability of data contributing to the primary endpoint or affect the rights, safety or well-being of a subject. Major protocol deviations will have additional reporting requirements.

When a major deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

The major protocol deviation criteria that will be summarized at the end of the study are as follows:

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

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

PD3 - Received wrong treatment or incorrect dose. For enfortumab vedotin, incorrect dose will be defined as less than or greater than 10% from the intended dose. For pembrolizumab, any dose of 1000 mg or greater will be considered incorrect dose.

PD4 - Received excluded concomitant treatment

The investigator will also assure that deviations meeting IRB/IEC and appropriate regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and appropriate regulatory authorities will be provided to the sponsor and maintained within the Trial Master File.

10.4 STUDY ORGANIZATION

10.4.1 Safety Monitoring Committee

A Safety Monitoring Committee (SMC), which consists of the sponsor and investigators, will be responsible for the review of study safety data for all cohorts on a periodic basis. The SMC may recommend whether the study should be terminated, modified or continue unchanged based on ongoing reviews of study safety data. Further details regarding responsibilities and membership requirements will be outlined in the SMC charter.

11 REFERENCES

American Cancer Society. Key Statistics for Lung Cancer. 2021a. https://www.cancer.org/cancer/lung-cancer/about/key-statistics.html. Accessed 09 Aug 2021.

American Cancer Society. Key Statistics for Esophageal Cancer. 2021b. https://www.cancer.org/cancer/esophagus-cancer/about/key-statistics.html. Accessed 09 Aug 2021.

Argiris A, Harrington KJ, Tahara M, Schulten J, Chomette P, Castro AF et al. Evidence-based treatment options in recurrent and/or metastatic squamous cell carcinoma of the head and neck. Front. Oncol. 2017;7:72

Aupérin A. Epidemiology of head and neck cancers: an update. Current Opinion in Oncology. 2020;32(3):178-186.

Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Eng J Med. 2017;376(11):1015–26.

Blank C, Brown I, Peterson AC, Spiotto M, Iwai Y, Honjo T, et al., PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res. 2004;64(3):1140-5.

Blot WJ, Mclaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston S, et al. Smoking and drinking in relation to oral and pharyngeal cancer. Cancer Res. 1988;48:3282–7.

Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or meta-static squamous cell carcinoma of the head and neck (KEYNOTE-048): A randomised, open-label, phase 3 study. Lancet 2019;394:1915–28.

Cardoso F, Harbeck N, Barrios CH, Bergh J, Cortes J, El Saghir N, et al. Research needs in breast cancer. Ann Oncol. 2017;28(2):208-17.

Challita-Eid PM, Satpayev D, Yang P, An Z, Morrison K, Shostak Y, et al. Enfortumab vedotin antibody-drug conjugate targeting Nectin-4 is a highly potent therapeutic agent in multiple preclinical cancer models. Cancer Res. 2016;76(10):3003-13.

Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 Associate with Immunoreceptor Tyrosine-Based Switch Motif of Programmed Death 1 upon Primary Human T Cell Stimulation, but Only Receptor Ligation Prevents T Cell Activation. The Journal of Immunology. 2004;173:945–54.

Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, et al; KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020;396(10265):1817-28.

Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomized study. Lancet. 2011;377:914-23.

Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci USA. 2010;107(9):4275-80.

Deng H, Shi H, Chen L, Zhou Y, Jiang J. Over-expression of Nectin-4 promotes progression of esophageal cancer and correlates with poor prognosis of the patients. Cancer Cell Int 2019;19:106.

Disis ML. Immune regulation of cancer. J Clin Oncol. 2010;28(29):4531-8.

Dudley ME, Wunderlich JE, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma. Journal of Clinical Oncology. 2005;0732-183.

Fabre-Lafay S, Monville F, Garrido-Urbani S, Berruyer-Pouyet C, Ginestier C, Reymond N, et al. Nectin-4 is a new histological and serological tumor associated marker for breast cancer. BMC Cancer 2007;7:73.

Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N. Engl. J. Med. 2016;375:1856–67.

Francisco, LM, Sage, PT, Sharpe, AH. The PD-1 pathway in tolerance and autoimmunity. Immunological Reviews. 2010;0105-2896.

Francisco JA, Cerveny CG, Meyer DL, Mixan BJ, Klussman K, Chace DF, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood. 2003;102(4):1458-65.

Global Cancer Observatory. International Agency for Research on Cancer. World Health Organization. https://gco.iarc.fr/ Accessed 18 Aug 2021.

Greene J, Hennessy B. The role of anthracyclines in the treatment of early breast cancer. J Oncol Pharm Pract 2015;201-12.

Greenwald, RJ, Freeman, GJ, Sharpe, AH. The B7 Family Revisited. Annual Reviews. 2005;23:515-48.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res. 2005;65(3):1089-96.

Hoimes CJ, Flaig TW, Milowsky MI, Friedlander TW, Bilen MA, Gupta S, et al. Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer. J Clin Oncol. 2023;41(1):22-31.

Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

Hurvitz S, Mead M. Triple-negative breast cancer: advancements in characterization and treatment approach. Curr Opin Obstet Gynecol. 2016;28(1):59-69.

Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40. doi: 10.1016/S0140-6736(21)00797-2. Epub 2021 Jun 5. PMID: 34102137.

Johnson DE, Burtness B, Leemans, CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers. 2020; 6(92).

Jones S, Winer E, Vogel C, Laufman L, hutchins L, O'Rourke M, et al. Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. J Clin Oncol. 1995;13(10):2567-74.

Kantar Group. CancerMPact® Treatment Architecture, Breast Cancer, US. Dec 2019 (proprietary report)

Kaufman PA, Awada A, Twelves C, Yelle L, Perex EA, Velikova G, et al. Phase III open-label randomized study of eribulin mesylate versus capecidabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and taxane. J Clin Onco. 2015;33(6):594-601.

Keam B, Machiels JP, Kim HR, Licitra L, Golusinski W, Gregoire V, et al. Pan-Asian adaptation of the EHNS-ESMO-ESTRO Clinical Practice Guidelines for the diagnosis, treatment and follow-up of patients with squamous cell carcinoma of the head and neck. ESMO Open. 2021 Dec;6(6):100309.

Keytruda (prescribing information). Merck Sharp & Dohme LLC. Rahway, NJ, USA. July 2021.

Leeman JE, Li JG, Pei X, Venigalla P, Zumsteg ZS, Katsoulakis E, et al. Patterns of treatment failure and postrecurrence outcomes among patients with locally advanced head and neck squamous cell carcinoma after chemoradiotherapy using modern radiation techniques. JAMA Oncol. 2017;3:1487–94

Machiels JP, René Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V; EHNS Executive Board. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020 Nov;31(11):1462-1475. doi: 10.1016/j.annonc.2020.07.011. Epub 2020 Oct 23. PMID: 33239190.

Masters GA, Temin S, Azzoli CG, Giaccone G, Baker S, Brahmer JR, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015;33(30):3488-3515.

National Cancer Institute. 2021a. Cancer Stat Facts: Common Cancer Sites. https://seer.cancer.gov/statfacts/html/common.html. Accessed 16 Aug 2021.

National Cancer Institute. Head and Neck Cancers. 29 Mar 2017. https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet. Accessed 05 Jun 2019.

National Comprehensive Cancer Network. Principles Of Systemic Therapy for Non-nasopharyngeal Cancers (Version 1.2023) https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed 10 Jan 2023.

National Comprehensive Cancer Network. 2021b. Non-small cell lung cancer (Version 5, 15 June 2021). http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 30 Aug 2021.

National Comprehensive Cancer Network. Gastric Cancer (Version 4, 03 Aug 2021c). https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed 05 Oct 2021.

National Comprehensive Cancer Network. Esophageal and Esophagogastric Junction Cancers (Version 4, 03 Aug 2021d). https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed 05 Oct 2021.

National Comprehensive Cancer Network. Bladder Cancer (Version 3, 2019). https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 01 Jul 2019.

Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res. 2007;13(7):2151-7.

Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27 (Supple 5):v1-v27.

Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci USA. 2001;98(24):13866-71.

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

Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 Receptors Inhibit T-Cell Activation by Distinct Mechanisms. Mol Cell Biol. 2005;9543-53.

Pembrolizumab (Keytruda®) Investigator's Brochure, Ed. 22. Merck Sharp & Dohme, Rahway, NJ, US. May 2022.

Perez EA, Lerzo G, Pivot X, Thomas E, Vahdat L, Bosserman L, et al. Efficacy and safety of ixabepilone (BMS-247550) in a phase II study of patients with advanced breast cancer resistant to anthracycline, a taxane, and capecitabine. J Clin Oncol. 2007;25:3407-14.

Petrylak D, Balar AV, O'Donnell PH, McGregor BA, Heath EI, Yu EY, et al. EV-201: Results of enfortumab vedotin monotherapy for locally advanced or metastatic urothelial cancer

previously treated with platinum and immune checkpoint inhibitors (NCT03219333). 2019 ASCO Annual Meeting.

Piccart, M. Circumventing de novo and acquired resistance to trastuzumab: new hope for the care of ErbB2-positive breast cancer. Clin Breast Cancer 2008;100-13.

Pilon-Thomas S, Mackay A, Vohra N, Mulé JJ. Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. J Immunol, 2010. 184(7):3442-9.

Plasilova ML, Hayse B, Killelea BK, Horowitz NR, Chagpar AB, Lannin DR. Features of triple-negative breast cancer: Analysis of 38,813 cases from the national cancer database. Medicine (Baltimore). 2016;95(35):e4614.

Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Ann Oncol 2010;1804-09.

Reymond N, Fabre S, Lecocq E, Adelaide J, Dubreuil P, and Lopez M. Nectin4/PRR4, a new afadin-associated member of the nectin family that trans-interacts with nectin1/PRR1 through V domian interaction. J Biol Chem 2001;43205-15.

Rikitake Y, Takai Y. Interactions of the cell adhesion molecule Nectin with transmembrane and peripheral membrane proteins for pleiotropic functions. Cell Mol Life Sci. 2008;65(2):253-63.

Riley, JL. PD-1 signaling in primary T cells. Immunological Reviews. 2009; 0105-2896

Robson M, Goessl C, Domchek S. Olaparib for Metastatic Germline BRCA-Mutated Breast Cancer. N Engl J Med. 2017;377(18):1792-3.

Rosenberg JE, Milowsky M, Ramamurthy C, Mar N, McKay RR, Friedlander T, et al. ESMO 12 Sep 2022: Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin (EV) monotherapy or in combination with pembrolizumab (P) in previously untreated cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC). ESMO 12 Sep 2022. Annals of Oncology.2022;33(suppl_7):S808-S869.

Rosenberg J, Sridhar SS, Zhang J, Smith D, Ruether D, Flaig TW, et al. Mature results from EV-101: a phase 1 study of enfortumab vedotin in patients with metastatic urothelial cancer. genitourinary cancers symposium of the American Society of Clinical Oncology. February 14-16, 2019. San Francisco, CA.

Sakisaka T, Ikeda W, Ogita H, Fujita N, Takai Y. The roles of nectins in cell adhesions: cooperation with other cell adhesion molecules and growth factor receptors. Current Opinion in Cell Biology 2007;19:593-602.

Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355:2542–50.

Schmid P, Chui SY, Emens LA. Atezolisumab and nab-paclitaxel in advanced triple-negative breast Cancer. N Engl J Med. 2019;380(10):987-988.

Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143-52.

Sheppard, K, Fitz, LJ, Lee, JM, Benander, C, George, JA, Wooter, J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3 signalosome and downstream signaling to PKC. FEBS Letters. 2004;0014-5793

Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021; 71:7.

Siewert J, Ott K. Are Squamous and Adenocarcinomas of the Esophagus the Same Disease? Seminars in Radiation Oncology. 2007;17(1):38-44

Socinski M, Obasaju C, Gandara D, Hirsch FR, Bonomi P, Bunn PA, et al. Current and emergent therapy options for advance squamous. Cell Lung Cancer 2018;165-183.

Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer. 2014;2:3.

Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, et al. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res. 2003;63(19):6501-5.

Takai Y, Ikeda W, Ogita H, and Rikitake Y. The immunoglobulin-like cell adhesion molecule nectin and its associated protein afadin. Annu Rev Cell Dev Biol. 2008;24:309-42.

Takano A, Ishikawa N, Nishino R, Masuda K, Yasui W, Inai K, et al. Identification of nectin-4 oncoprotein as a diagnostic and therapeutic target for lung cancer. Cancer Res. 2009;69(16):6694-6703.

Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008;359:1116–27.

Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer--preclinical background: CTLA-4 and PD-1 blockade. Semin Oncol. 2010;37(5):430-9.

Windon MJ, D'Souza G, Rettig EM, Westra WH, van Zante A, Wang SJ, et al. Increasing prevalence of human papillomavirus-positive oropharyngeal cancers among older adults. Cancer 2018;124:2993–9.

World Health Organization. Cancer Fact Sheet. 03 Mar 2021a. https://www.who.int/news-room/fact-sheets/detail/cancer. Accessed 16 Aug 2021.

World Health Organzation. Breast Cancer Fact Sheet. 26 Mar 2021b. https://www.who.int/news-room/fact-sheets/detail/breast-cancer. Accessed 16 Aug 2021.Wu AW, Ji JF. Adenocarcinoma of esophagogastric junction requires a clearer definition. Transl Gastrointest Cancer 2013;2:5-9.

Yoon H. Initial systemic therapy for locally advanced unresectable and metastatic esophageal and gastric cancer. 30 Jun 2021(a). https://www.uptodate.com/contents/initial-systemic-therapy-

for-locally-advanced-unresectable-and-metastatic-esophageal-and-gastric-cancer. Accessed 18 Aug 2021.

Yoon H. Progressive, locally advanced unresectable, and metastatic esophageal and gastric cancer: Approach to later lines of systemic therapy. 09 Jul 2021(b). https://www.uptodate.com/contents/progressive-locally-advanced-unresectable-and-metastatic-esophageal-and-gastric-cancer-approach-to-later-lines-of-systemic-therapy/print. Accessed 18 Aug 2021.

Zhang X, Schwartz J-CD, Guo X, Bhatia S, Bhatia S, Cao E,et al. Structural and Functional Analysis of the Costimulatory Receptor Programmed Death-1. Immunity.2004;20(3):337-47

Zhang Y, Chen P, Yin W, Ji Y, Shen Q, Ni Q et al. Nectin-4 promotes gastric cancer progression via the PI3K/AKT signaling pathway. Human Pathology 2018a;72:107-116.

Zhang Y, Zhang J, Shen Q, Yin W, Huang H, Liu Y et al. High expression of Nectin-4 is associated with unfavorable prognosis in gastric cancer. Oncology Letters 2018b;15:8789-8795.

Zhou H, Lee JJ, Yuan Y. BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints. Stat Med. 2017;36(21):3302-3314.

12 APPENDICES

12.1 Ethical, Regulatory and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

12.1.2 Institutional Review Board/Independent Ethics Committee/Competent Authorities

GCP requires that the protocol, any protocol amendments, investigator's brochure, ICF and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB/IEC. The IRB/IEC will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB/IEC approval of the protocol, ICF and subject information and/or advertising, as relevant, will be obtained prior to initiation of any study-specific procedures.

Any substantial amendments to the protocol will require competent authority and IRB/IEC approval before implementation, except for changes necessary to eliminate an immediate hazard to subjects.

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 study site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, EU Regulation No. 536/2014 for studies (if applicable), and all other applicable local regulations.

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or nonsubstantial amendments. Depending on the nature of the amendment, either IRB/IEC or competent authority approval or notification may be required. The changes will become effective only after the approval of the sponsor, investigator, IRB/IEC and appropriate regulatory authorities.

Amendments to this protocol must be signed by the sponsor and investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the ICF, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new ICF must also be forwarded to the sponsor.

12.1.4 Informed Consent of Subjects

12.1.4.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the ICF will be reviewed, signed and dated by the subject or his/her guardian or legal representative, the person who administered the ICF and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that the ICF was signed prior to any study-related procedures and that the subject received a signed copy of the ICF.

The signed ICFs will be retained by the investigator and made available (for review only) to the study monitor, auditor and appropriate regulatory authorities and other applicable individuals upon request.

12.1.4.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

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

12.1.5 Source Documents

Source data must be available at the study site to document the existence of the subjects 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 subject.

The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, and/or drug accountability.

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 subject file and be available for archiving.

12.1.6 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data CRFs and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US study sites, 2 years after approval of the NDA or discontinuation of the IND). The sponsor will notify the study site/investigator if the NDA/MAA/J-NDA is approved or if the IND/investigational medicinal product dossier/CHIKEN TODOKE is discontinued. The investigator agrees to obtain the sponsor’s agreement prior to disposal, moving or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subject’s medical records and/or study progress notes.

For investigational sites located in Japan, 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, or 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, subject files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips, 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 1 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 investigational product and other duties related to the study. Procedure for controlling the investigational product, drug inventory and accountability record, vouchers for the receipt and return of the investigational product, and the prescriptions for concomitant medications

12.1.7 Subject Confidentiality and Privacy

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

The sponsor shall not disclose any confidential information on subjects 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 subject'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 subject's right to protection against invasion of privacy. Only a subject identification number will identify subject 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.

12.1.8 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 drug 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.

12.1.9 Insurance of Subjects and Others

If a subject suffers any study-related injury, the sponsor will compensate the subject 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 subject 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 subject 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.

12.1.10 Signatory Investigator for Clinical Study Report

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 hard-lock.

12.2 Procedure for Study Quality Control

12.2.1 Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the study to ensure that the rights, safety and well-being of subjects are protected, the study is properly conducted in adherence to the current protocol and GCP and the study data reported by the investigator/subinvestigator are accurate, complete and verifiable with the source. The sponsor is responsible for assigning the study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12.2.2 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO, as well as inspections from the IRB/IEC and appropriate regulatory authorities. In these instances, they must provide all study-related records including source documents when they are requested by the sponsor monitors and auditors, the CRO, the IRB/IEC or appropriate regulatory authorities. The confidentiality of the subject's identity shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

12.2.3 Data Management

Data management will be coordinated by the Data Science department of the sponsor in accordance with the SOPs for data management. All study-specific processes and definitions will be documented by data management. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and the World Health Organization (WHO) Drug Dictionary, respectively.

12.2.4 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.

Quality tolerance limits (QTLs) will be predefined in the applicable plan(s) to identify systematic issues that can impact subject 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.

12.3 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 schedules of assessments. Pregnancy test results must confirm that the subject 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 1 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 1 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 subject's medical records, medical examination or medical history interview.

CONTRACEPTION GUIDANCE FOR FEMALE SUBJECTS OF CHILDBEARING POTENTIAL

Female subjects of childbearing potential are eligible for participation in the study if they agree to use a condom plus 1 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 investigational product 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.
- Male is sterile due to a bilateral orchiectomy or radical cystoprostatectomy/removal of seminal vesicles
- 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 subject. 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 subjects participating in clinical studies.

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

Male subjects 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 subjects who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy require use one form of highly effective methods of contraception

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

12.4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

12.4.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered an investigational product (IP), and which does not necessarily have to have a causal relationship with this treatment. 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 IP whether or not considered related to the IP.

12.4.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, biochemistry) 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 subject'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.

12.4.1.2 Potential Cases of Drug-induced Liver Injury

Refer to [Appendix 12.5 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 [Appendix 12.5 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 12.4.5 Reporting Procedures for Serious Adverse Events].

12.4.2 Definition of Serious Adverse Events

An AE is considered "serious" if, in the view of either the investigator or sponsor, the event:

- Results in death
- Is life-threatening (An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death; it does not include an AE that, had it occurred in a more severe form, might have caused death).
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect

- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE)
- Other medically important events (defined in paragraph below)

Medical and scientific judgment should be exercised in deciding whether expedited 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.4.3 Criteria for Causal Relationship to Investigational Product

A medically qualified investigator is obligated to assess the relationship between IP and each occurrence of each (S)AE. This investigator will use medical judgment as well as the reference safety information to determine the relationship. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

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 subject been administered IP?
- Plausibility (i.e., could the event have been caused by the suspect drug? 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 laboratory investigation supports the assessment of the relationship between the (S)AE and the IP (e.g., based on values pretreatment, during and posttreatment)
- 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
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausible temporal relationship between exposure to the IP and (S)AE onset and/or resolution will be provided. Did the (S)AE occur in a reasonable temporal relationship to the administration of the IP?

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 assesses causality for every event before the initial transmission of the SAE data to the sponsor. 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.

12.4.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the NCI-CTCAE guidelines Version 4.03. The items that are not stipulated in the NCI-CTCAE Version 4.03 will be assessed according to the criteria below and entered into the eCRF:

Table 12 Grading Scale Defining the Severity of an Adverse Event

Grade	Assessment Standard
1 - Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2 - Moderate	Minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL†
3 - Severe	Medically significant but not immediately life-threatening, hospitalization or prolonged hospitalization indicated; disabling; limiting selfcare 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.

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

12.4.5 Reporting Procedures for Serious Adverse Events

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

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

For contact details, see [Contact Details of Sponsor's Key Personnel]. Fax or email the SAE/special situations 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]
International fax number: +44-800-417-5263
Email: safety-us@astellas.com

For investigational sites located in Japan:

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

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU 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.

JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the SAE/special situations worksheet to:

Astellas Pharma Inc. – Japan
Pharmacovigilance
Fax number: +81-(0)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 situations worksheet and on the eCRF.

The following minimum information is **required**:

- International study number/study number
- Subject 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., suspected unexpected serious adverse reaction [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.

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 subject.

12.4.6 Reporting Procedures for Special Situations

12.4.6.1 Pregnancy

If a female subject 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 12.4.5 Reporting Procedures for Serious Adverse Events] using the pregnancy reporting form as a special situation and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing and report the information to the sponsor according to the timelines in [Section 12.4.5 Reporting Procedures for Serious Adverse Event**s**] using the pregnancy reporting form as a special situation.

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 subject as an AE in the eCRF or SAE per [Section 12.4.5 Reporting Procedures for Serious Adverse Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the SAE worksheet.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- "Spontaneous abortion" includes 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).

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.

12.4.6.2 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 subject), overdose or "off-label use" (i.e., use outside of what is stated in the protocol) is suspected, refer to [Section 10.3 Major Protocol Deviations]. 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 12.4.5 Reporting Procedures for Serious Adverse Events] together with the details of the medication error, overdose and/or "off-label use."

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

12.4.6.3 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 situations 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 12.4.5 Reporting Procedures for Serious Adverse Events] together with details of the misuse or abuse of the IP.

12.4.6.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the IP of study site personnel while preparing it for administration to the subject) to the IP occurs, the investigator must forward the special situations 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.

12.4.6.5 (Suspicion of) Transmission of Infectious Agent

If transmission of an infectious agent associated with the IP is suspected, the investigator must forward the special situations 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 12.4.5 Reporting Procedures for Serious Adverse Events] together with the details of the suspected transmission of infectious agent.

12.4.6.6 Suspected Drug-drug Interaction

If a drug-drug interaction associated with the IP is suspected, the investigator must forward the special situations 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 12.4.5 Reporting Procedures for Serious Adverse Events] together with details of the suspected drug-drug interaction.

12.5 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 subject enrolled in a study with active drug therapy and who reveals an increase of serum aminotransferases (AT) to > 3 × ULN (to > 5 × ULN in subjects with liver metastases) or total bilirubin > 2 × ULN should undergo detailed testing for liver enzymes (including at least 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. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

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

Table 13 Moderate and Severe Liver Abnormalities

	ALT or AST		TBL
Moderate	> 3 × ULN (in subjects without liver metastases), > 5 × ULN (in subjects with liver metastases)	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 subject 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 (in the absence of liver metastases)
- 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 > 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 those 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). Subjects 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 then weekly or less if abnormalities stabilize or the investigational product has been discontinued and the subject 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 subjects for whom severe hepatic liver function abnormalities possibly attributable to investigational product 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 in 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 subjects 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, including dose, 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 subject'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, 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, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject'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 (in subjects without liver metastases)
- 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 subjects 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 subject with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

Hy's Law Definition:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by a higher rate than control of people with 3 × AT elevations over the ULN (2 × elevations are too common in treated and untreated subjects to be discriminating).
2. Cases of increased bilirubin (to at least 2 × ULN) in people with concomitant AT elevation to at least 3 × ULN (but it is almost invariably higher) 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:

FDA Guidance for Industry:

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 subjects showing such AT elevations, often with AT levels much greater than 3 × ULN, 1 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.

References

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

12.6 List of Cautionary Concomitant Medications

The following list describes medications and foods that are common strong inhibitors of CYP3A4 that should be used with caution or closely monitored. This list should not be considered all inclusive; consult individual drug labels for specific information. If there are concerns or questions about concomitant use of any drugs listed below, discussion with the sponsor is encouraged.

Strong CYP3A4 Inhibitors
boceprevir
cobicistat
conivaptan
danoprevir/ ritonavir
elvitegravir/ ritonavir
grapefruit juice
indinavir/ ritonavir
itraconazole
ketoconazole
lopinavir/ritonavir
paritaprevir/ ritonavir/ (ombitasvir and/or dasabuvir)
posaconazole
ritonavir
saquinavir/ ritonavir
telaprevir
tipranavir/ritonavir
troleandomycin
voriconazole

CYP: cytochrome

Note: Any additional strong inhibitors of CYP3A4 that are identified or become commercially available while the clinical study in ongoing are also applicable.

12.7 Laboratory Assessments

Laboratory tests will be performed according to the schedules of assessments and sent to the local laboratory for analysis.

Table 14 Clinical Laboratory Tests

Panel/Assessments	Parameters to be Analyzed
Hematology	Hematocrit (Hct) Hemoglobin (Hb) Platelets Red blood cell count (RBC) White blood cell count (WBC) White blood cell count differential (Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes) Absolute neutrophil count (ANC)
Biochemistry	Albumin (Alb) Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bicarbonate (HCO3) Bilirubin (total and direct) Blood urea nitrogen (BUN) Calcium Corrected (CCa) Chloride (Cl) Creatinine Glucose Hemoglobin A1c (HbA1c, screening and EOT only) Lactate dehydrogenase (LDH) Magnesium (Mg) Phosphate (P) Potassium (K) Sodium (Na) Total protein (TP) Uric Acid Lipid panel (screening only), including: Total cholesterol (T chol) High-density lipoprotein cholesterol (HDL-C) Low-density lipoprotein cholesterol (LDL-C) Triglycerides (Trig)
Thyroid Function Tests	Triiodothyronine (T3) or Free Triiodothyronine (FT3) Free thyroxine (FT4) Thyroid stimulating hormone (TSH)
Coagulation (Cohort 9 only)	INR PT PTT
Pregnancy Test	Serum or urine β-human Chorionic Gonadotropin (hCG). See Schedules of Assessments for women of childbearing potential.
Note: Fasting blood samples are required at screening and on cycle 1 day 8 only.	

12.8 Pharmacogenomic Analysis with Banked Sample (Optional)

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring differences in a subject's gene and/or expression of genes based on genetic variation may impact what treatment options are best suited for the subject. 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 or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject 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.

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

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in the PGx substudy. Subjects 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

Subjects who consent to participate in this substudy will provide 4 to 6 mL of whole blood sample per Astellas' instructions. Each sample will be identified by the unique subject number. Samples will be shipped to a design 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.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hard-lock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject'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 SUBJECTS

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 subjects, 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.

12.9 RECIST Version 1.1

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer. 2009;45:228-47.

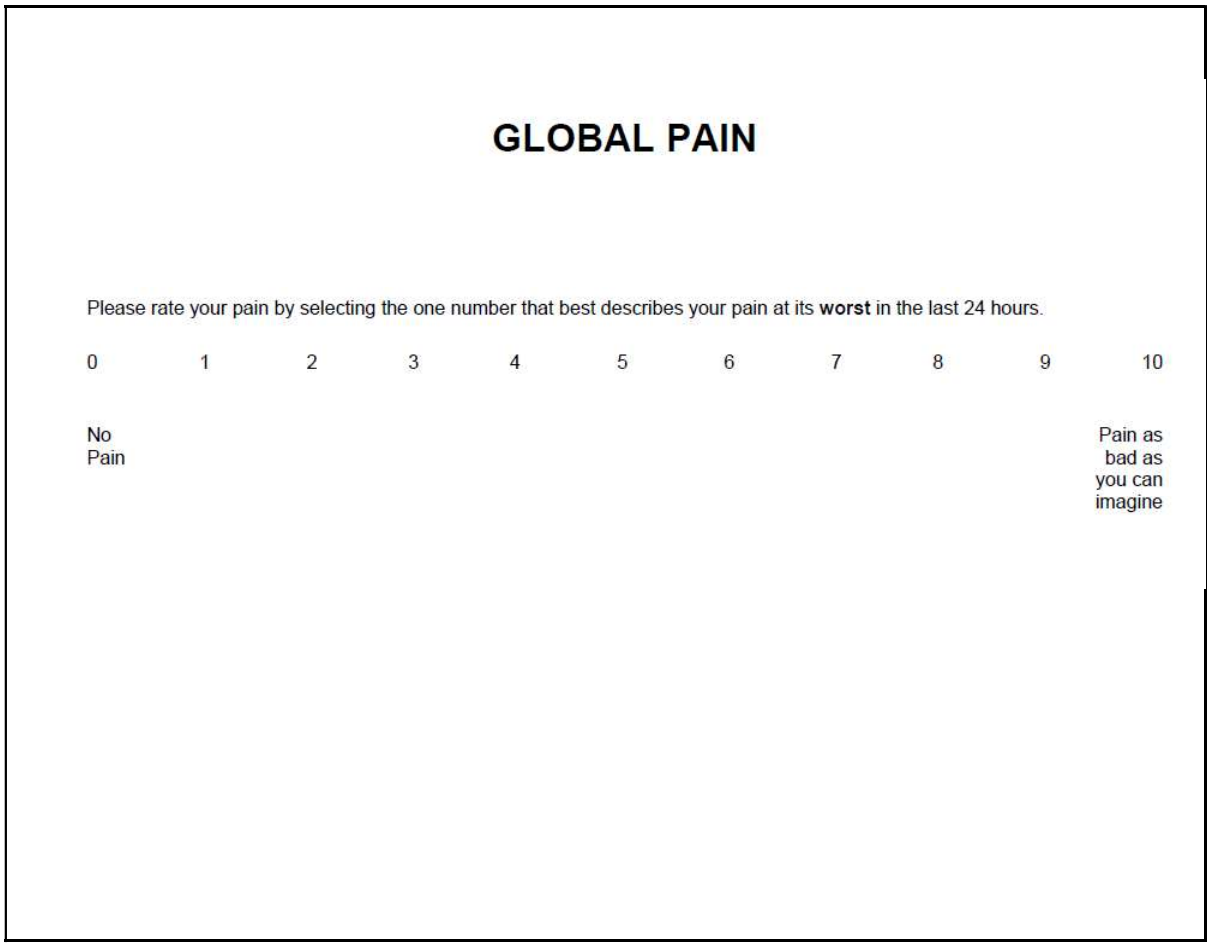
12.10 Eastern Cooperative Oncology Group Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease 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 selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

ECOG: Eastern Cooperative Oncology Group

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

12.11 Global Pain Assessment



12.12 EQ-5D-5L

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

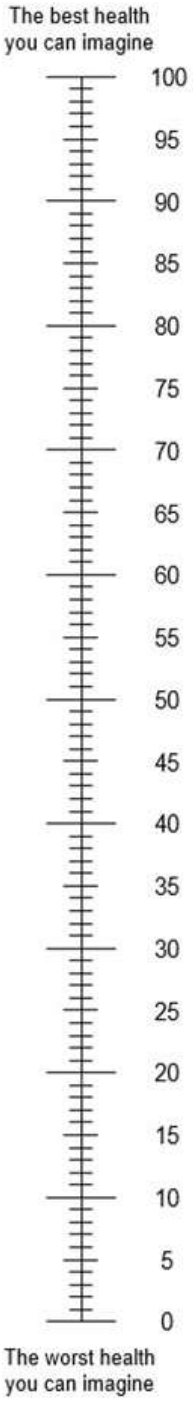
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



12.13 EORTC QLQ H&N43

EORTC QLQ – H&N43

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had pain in your throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you choked when swallowing?	1	2	3	4
39. Have you had problems with your teeth?	1	2	3	4
40. Have you had problems because of losing some teeth?	1	2	3	4
41. Have you had problems opening your mouth wide?	1	2	3	4
42. Have you had a dry mouth?	1	2	3	4
43. Have you had sticky saliva?	1	2	3	4
44. Have you had problems with your sense of smell?	1	2	3	4
45. Have you had problems with your sense of taste?	1	2	3	4
46. Have you had problems with coughing?	1	2	3	4
47. Have you had problems with hoarseness?	1	2	3	4
48. Have you had problems with your appearance?	1	2	3	4
49. Have you felt less physically attractive as a result of your disease or treatment?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
50. Have you felt dissatisfied with your body?	1	2	3	4
51. Have you had problems eating?	1	2	3	4
52. Have you had problems eating in front of your family?	1	2	3	4
53. Have you had problems eating in front of other people?	1	2	3	4
54. Have you had problems enjoying your meals?	1	2	3	4
55. Have you had problems talking to other people?	1	2	3	4
56. Have you had problems talking on the telephone?	1	2	3	4
57. Have you had problems talking in a noisy environment?	1	2	3	4
58. Have you had problems speaking clearly?	1	2	3	4
59. Have you had problems going out in public?	1	2	3	4
60. Have you felt less interest in sex?	1	2	3	4
61. Have you felt less sexual enjoyment?	1	2	3	4
62. Have you had problems raising your arm or moving it sideways?	1	2	3	4
63. Have you had pain in your shoulder?	1	2	3	4
64. Have you had swelling in your neck?	1	2	3	4
65. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
66. Have you had a rash?	1	2	3	4
67. Has your skin changed colour?	1	2	3	4
68. Have you worried that your weight is too low?	1	2	3	4
69. Have you worried about the results of examinations and tests?	1	2	3	4
70. Have you worried about your health in the future?	1	2	3	4
71. Have you had problems with wounds healing?	1	2	3	4
72. Have you had tingling or numbness in your hands or feet?	1	2	3	4
73. Have you had problems chewing?	1	2	3	4

12.14 PRO-CTCAE Questions

NCI-PRO-CTCAE® CUSTOM SURVEY
Item subset derived from PRO-CTCAE® Item Library Version 1.0
English
Form Created on 10-January-2023
https://healthcaredelivery.cancer.gov/pro-ctcae/builder.html

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

2a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
2b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

OTHER SYMPTOMS					
Do you have any other symptoms that you wish to report?					
O Yes	O No				
Please list any other symptoms:					
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe

4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? O None O Mild O Moderate O Severe O Very Severe

12.15 FACT-G

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

12.16 List of Abbreviations and Definition of Key Study Terms

List of Abbreviations

Abbreviations	Description of abbreviations
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APGD	Astellas Pharma Global Development Inc.
aPTT	activated partial thromboplastin
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
AST	aspartate aminotransferase
AT	aminotransferase
ATA	antitherapeutic antibodies
AUST	Astellas US Technologies
BICR	blinded independent central review
BOP2	Bayesian optimal design for phase 2
BOR	best overall response
CA	competent authorities
CD28	cluster of differentiation 28
CDK	cyclin-dependent kinase
cfDNA	circulating free deoxyribonucleic acid
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP	cytochrome
DCR	disease control rate
DLT	dose-limiting toxicity

Abbreviations	Description of abbreviations
dMMR	mismatch repair deficient
DOR	duration of response
DPD	data protection directive
EAC	esophageal adenocarcinoma
ECD	extracellular domain
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European economic area
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	end of treatment
EQ-5D-5L	EuroQOL 5-dimensions
ER	estrogen receptor
ESCC	esophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	full analysis set
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
FU	fluorouracil
GCP	Good Clinical Practice
GEAC	gastroesophageal adenocarcinoma
GEJ	gastroesophageal junction
GFR	glomerular filtration rate
GI	gastrointestinal
GMP	Good Manufacturing Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HDL-C	high-density lipoprotein cholesterol
HER2	human epidermal growth factor receptor 2
HER2-	human epidermal growth factor receptor 2-negative
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus

Abbreviations	Description of abbreviations
HR	hazard ratio
HR+	Hormone receptor positive
HRQOL	health-related quality of life
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	confirmed progressive disease (based on iRECIST guidelines)
IEC	Independent Ethics Committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IgG4	immunoglobulin G4
IHC	immunohistochemistry
ILD	interstitial lung disease
imAE	immune-mediated adverse event
IND	investigational new drug
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
iRECIST	modified RECIST v1.1 for immune-based therapeutics
IRR	infusion-related reactions
IRT	Interactive response technology
ISS	integrated summary of safety
iUPD	unconfirmed progressive disease (based on iRECIST guidelines)
LA-CRF	liver abnormality case report form
LDL-C	low-density lipoprotein cholesterol
mAbs	monoclonal antibodies
MCBS	Magnitude of Clinical Benefit Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MMR	mismatch repair
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
mUC	metastatic urothelial cancer
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute-
ND	no data
NDA	new drug application

Abbreviations	Description of abbreviations
NE	not evaluable
NGS	next-generation sequencing
NLNT	New Lesion-Non-Target
NLT	New Lesion-Target
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OPC	oropharngeal cancer
ORR	objective response rate
OS	overall survival
PARP	poly ADP ribose polymerase
PBMC	peripheral blood mononuclear cells
PBPK	physiologically-based pharmacokinetics
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PGx	pharmacogenomic
PK	pharmacokinetics
PKAS	pharmacokinetics analysis set
PR	partial response
PRO	patient reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
QA	quality assurance
QC	quality control
QOL	quality of life
QTL	quality tolerance limits
R/M	recurrent/metastatic
RANK	receptor activator of nuclear factor kappa-B
RECIST	Response Evaluation Criteria in Solid Tumors
RES	response evaluable set
ROS	reactive oxygen species
(S)AE	serious adverse event or adverse event
SAE	serious adverse event
SAF	safety analysis set

Abbreviations	Description of abbreviations
SAP	statistical analysis plan
SCAR	severe cutaneous adverse reactions
SD	stable disease
SDRIFE	symmetrical drug-related intertriginous and flexural exanthema
SJS	Stevens-Johnson Syndrome
SMC	Safety Monitoring Committee
SOC	system organ class
SOD	sum of diameters
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
T1DM	type 1 diabetes mellitus
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
t_{max}	time of maximum concentration
TMDD	target-mediated drug disposition
TNBC	triple negative breast cancer
TTR	time to response
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USM	urgent safety measure
WHO	World Health Organization
WOCBP	women of childbearing potential

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	Assessments of subjects 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 subject into a study after screening.
Intervention	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 QOL, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test product or comparative drug (sometimes without randomization) is given to a subject and continues until the last assessment after completing administration of the test product or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained AEs and/or survival are done in this period.
Screening	A process of active consideration of potential subjects for enrollment in a study.
Screen failure	Potential subject who signed the ICF but did not meet 1 or more criteria required for participation in the study and was not enrolled.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent form until just before the test product or comparative drug (sometimes without randomization) is given to a subject.
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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