STATISTICAL ANALYSIS PLAN

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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. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest for enfortumab vedotin
AEOSI	adverse event of special interest for pembrolizumab
Alb	albumin
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
ATC	anatomical therapeutic chemical
BICR	blinded independent central review
BMI	body mass index
BOP2	Bayesian optimal design for phase 2
BOR	best overall response
BUN	blood urea nitrogen
Ca	calcium
CDK	cyclin-dependent kinase
CI	confidence interval
Cl	chloride
CMQ	customized MedDRA query
CNS	central nervous system
CPI	checkpoint inhibitor
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOT	end of treatment
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQOL 5-dimensions
ER	estrogen receptor
EAC	Esophageal adenocarcinoma
ESCC	Esophageal squamous cell carcinoma

Abbreviations	Description of abbreviations
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	full analysis set
GEJ	gastroesophageal junction
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
hCG	human chorionic gonadotropin
HCO3	bicarbonate
Hct	hematocrit
HDL-C	high-density lipoprotein cholesterol
HER2-	human epidermal growth factor receptor 2-negative
HLGT	high level group term
HLT	high level term
HNSCC	head and neck squamous cell carcinoma
HR+	hormone receptor positive
HRQOL	health-related quality of life
iBOR	best overall response per iRECIST
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	confirmed progressive disease (based on iRECIST guidelines)
iDCR	disease control rate per iRECIST
iDOR	duration of response per iRECIST
IHC	immunohistochemical
ILD	interstitial lung disease
IND	investigational new drug
INR	international normalized ratio
iORR	objective response rate per iRECIST
iPFS	progression-free survival per iRECIST
iRECIST	modified RECIST 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	stable disease per iRECIST
iUPD	unconfirmed progressive disease (based on iRECIST guidelines)
K	potassium
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
Mg	magnesium
MMAE	monomethyl auristatin E
MSD	Merck Sharp & Dohme LLC, Rahway, NJ, USA
Na	sodium
NCI	National Cancer Institute
NCI-ODWG	National Cancer Institute - organ dysfunction working group
ND	no data
NSCLC	non-small cell lung cancer
ORR	objective response rate

Abbreviations	Description of abbreviations
OS	overall survival
P	phosphate
PARP	poly adenosine diphosphate-ribose polymerase
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PKAS	pharmacokinetics analysis set
PR	partial response
PRO	patient reported outcome
PT	preferred term
PT	prothrombin time
PTT	partial thromboplastin time
QOL	quality of life
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RES	response evaluable set
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SD	stable disease
SD	standard deviation
SMC	safety monitoring committee
SMQ	standard MedDRA query
SOC	system organ class
SOD	sum of diameters
SSQ	sponsor specific query
TEAE	treatment-emergent adverse event
TLF	table listing and figure
TNBC	triple negative breast cancer
TP	total protein
TPS	tumor proportion score
TTR	time to response
ULN	upper limit of normal
VAS	visual acuity score
WBC	white blood cell
WHO	World Health Organization

List of Key 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.

1 INTRODUCTION

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

The final SAP will be approved prior to the primary database hardlock.

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

2 STUDY OBJECTIVE(S) AND DESIGN

2.1 Study Objectives

Cohorts 1 to 8:

Primary Objective:

To determine the antitumor activity of enfortumab vedotin as measured by confirmed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 by investigator assessment.

Secondary Objectives:

- To assess other measures of antitumor activity of enfortumab vedotin per RECIST Version 1.1 by investigator assessment
- To assess the overall survival (OS)
- To assess the safety and tolerability of enfortumab vedotin

Exploratory Objectives:

- 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)

Cohort 9:

Primary Objective:

To determine the antitumor activity of enfortumab vedotin in combination with pembrolizumab as measured by confirmed ORR per RECIST Version 1.1 by investigator assessment.

Secondary Objectives:

- To assess other measures of antitumor activity of enfortumab vedotin in combination with pembrolizumab per RECIST Version 1.1 by investigator assessment
- To assess the OS of enfortumab vedotin in combination with pembrolizumab
- To assess the safety and tolerability of enfortumab vedotin in combination with pembrolizumab

Exploratory Objectives:

- 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 MMAE
- To assess the immunogenicity of enfortumab vedotin
- To evaluate the treatment effect of enfortumab vedotin in combination with pembrolizumab on QOL
- To assess measures of antitumor activity of enfortumab vedotin in combination with pembrolizumab per RECIST Version 1.1 by BICR
- To assess measures of antitumor activity of enfortumab vedotin in combination with pembrolizumab per iRECIST by investigator assessment

2.2 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.

Cohort 1: Hormone receptor positive/ human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer; or

Cohort 2: Triple negative breast cancer (TNBC); or

Cohort 3: Squamous non-small cell lung cancer (Squamous NSCLC); or

Cohort 4: Non-squamous non-small cell lung cancer (Non-squamous NSCLC); or

Cohort 5: Head and neck cancer; or

Cohort 6: Gastric or gastroesophageal junction (GEJ) or esophageal cancer (reallocated to Cohort 7 or 8)

Cohort 7: Gastric adenocarcinoma or esophageal adenocarcinoma (EAC) or gastroesophageal junction (GEJ) adenocarcinoma

Cohort 8: Esophageal squamous cell carcinoma (ESCC)

Cohort 9: Previously untreated head and neck squamous cell carcinoma (HNSCC)

Subjects enrolled into Cohort 6 will be reallocated based on disease type and histology into Cohort 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 (complete response [CR] and partial response [PR] per Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.1) is less than the prespecified minimum number of responders at stage 1, the enrollment of the cohort may stop; otherwise, the enrollment will continue until the planned size of the cohort is reached.

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

Starting at cycle 1, subjects in cohorts 1 to 8 will receive enfortumab vedotin on days 1, 8, and 15 of every 28-day cycle until one of the treatment discontinuation criteria is 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 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 (63 days ± 7 days) from the first dose of study treatment and then every 6 weeks (36 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. After 18 months on study treatment, the frequency of disease assessment will be reduced to every 9 weeks (± 7 days). Subjects with unconfirmed progressive disease per iRECIST guidelines (iUPD) [Seymour et al, 2017] who are clinically stable may continue on study treatment until progression is confirmed by the investigator (confirmed progressive disease [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 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 be sent to the independent review facility in a timely manner. Central images may be read for a cohort after the minimum number of responders (confirmed ORR) at stage 1 based on the 2-stage BOP2 design are met per investigator assessment. 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.

Response (CR or PR) must be confirmed with a repeat imaging scan 4 weeks (28 days + 7-day window) after first response.

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.

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.

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

2.3 Randomization

This is an open-label non-randomized study. Subject enrollment and dispensation of enfortumab vedotin will be performed via the interactive response technology (IRT) system.

3 SAMPLE SIZE

The planned sample size for cohorts 1 to 8 is approximately 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 to have 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 BOP2, the enrollment of a cohort maybe stopped after interim analysis.

4 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 (1995) and E9 (1998), the following analysis sets will be used for the analyses.

The determination of whether subjects are included or excluded from the analysis sets will be made prior to database hardlock.

4.1 Full Analysis Set

The full analysis set (FAS) consists of all enrolled subjects who receive any amount of study drug. The FAS will be used for primary analyses on overall survival (OS) and progression-free survival (PFS), as well as summaries for demographic, baseline characteristics and patient reported outcomes (PRO).

4.2 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 either have at least 2 postbaseline response assessments or are no longer in the follow-up of response at the time of analysis. The RES will be used for the primary analysis set for the response related efficacy analyses, i.e., ORR, duration of response (DOR) and disease control rate (DCR), as well as demographic and baseline characteristics.

4.3 Safety Analysis Set

The safety analysis set (SAF) consists of all subjects who receive any amount of study drug, and thus is equivalent to the FAS. The SAF will be used for summaries of the safety data as well as study drug exposure, prior and concomitant medications, and posttreatment medications.

4.4 Pharmacokinetics Analysis Set

The pharmacokinetics analysis set (PKAS) is a subset of the FAS. It consists of subjects who receive 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.

The PKAS is used for all tables and graphical summaries of the pharmacokinetic data.

5 SUMMARY OF ENDPOINTS

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is confirmed ORR per RECIST Version 1.1 by investigator assessment.

Confirmed ORR is defined as the proportion of subjects whose best overall response (BOR) is a confirmed CR or confirmed PR according to RECIST Version 1.1 as assessed by investigator. Definition of BOR is specified in Section 5.2.5.1. The primary analysis population for confirmed ORR is RES.

5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include duration of response (DOR) per RECIST Version 1.1 by investigator assessment, disease control rate (DCR) per RECIST Version 1.1 by investigator assessment, PFS per RECIST Version 1.1 by investigator assessment, OS and safety endpoints.

5.2.1 Duration of Response Per Investigator Assessment

DOR is defined as the time from the date of first documented response (CR or PR that is subsequently confirmed) as assessed by investigator to the date of first documented radiological disease progression (PD) per RECIST Version 1.1 or death due to any cause, whichever occurs first. DOR will only be calculated for subjects who achieved a confirmed CR or PR. DOR will be censored as the following:

- If a subject has neither PD nor death, DOR will be censored at the date of last evaluable radiological tumor assessment.
- If a subject starts a new anti-cancer treatment before any PD event or death, DOR will be censored at the date of last evaluable radiological tumor assessment prior to the date of new anti-cancer treatment.
- If a subject has PD or death immediately after two or more consecutive missed radiological tumor assessments, DOR will be censored at the last evaluable radiological tumor assessment prior to two or more missed radiological tumor assessments.
- If a subject does not have subsequent evaluable postbaseline radiological assessment, DOR will be censored at the first CR/PR date.

For a subject who is censored, the last evaluable radiological tumor assessment refers to the subject's last radiological tumor assessment where the response is CR, PR or SD.

New anti-cancer treatment includes therapies captured on new anti-cancer therapy eCRF and new radiation/palliative radiation therapies captured on new radiation therapy eCRF that will impact target and/or non-target lesions.

DOR (in months) will be calculated as:

[(Date of documented progression or death or censoring) – (Date of the first CR/PR that is subsequently confirmed) + 1] / 30.4375

When a cutoff date is applied to DOR analysis, tumor assessment, death and new anti-cancer treatment occurring after the cutoff date will be excluded from the analysis.

The primary analysis population for DOR is RES who achieved a confirmed CR or PR.

5.2.2 Disease Control Rate per Investigator Assessment

DCR is defined as the proportion of subjects with BOR of confirmed CR or confirmed PR or stable disease (SD), per RECIST Version 1.1 as assessed by investigator. Definition of BOR is specified in Section 5.2.5.1. The primary analysis population for DCR is RES.

5.2.3 Progression-free Survival per Investigator Assessment

PFS is defined as the time from the date of first dose of study drug to the date of first documented radiological disease progression (PD) per RECIST Version 1.1 by investigator assessment or death due to any cause, whichever comes first. PFS will be censored as the following:

- If a subject has neither PD nor death, PFS will be censored at the date of last evaluable radiological tumor assessment.
- If a subject starts a new anti-cancer treatment before any PD event or death, PFS will be censored at the date of last evaluable radiological tumor assessment prior to the date of new anti-cancer treatment.
- If a subject has PD or death immediately after two or more consecutive missed radiological tumor assessments, DOR will be censored at the last evaluable radiological tumor assessment prior to two or more missed radiological tumor assessments.
- If a subject does not have evaluable postbaseline radiological assessment, PFS will be censored at the first dose date of study drug.

For a subject who is censored, the last evaluable radiological tumor assessment refers to the subject's last radiological tumor assessment where the response is CR, PR or SD.

New anti-cancer treatment includes therapies captured on new anti-cancer therapy eCRF and new radiation/palliative radiation therapies captured on new radiation therapy eCRF that will impact target and/or non-target lesions.

PFS (in months) will be calculated as:

[(Date of documented disease progression or death or censoring) – (Date of first dose of study drug) + 1] / 30.4375

When a cutoff date is applied to PFS analysis, tumor assessment, death and new anti-cancer treatment occurring after the cutoff date will be excluded from the analysis.

The primary analysis population for PFS is FAS.

5.2.4 Overall Survival

OS is defined as the time from the date of first dose of study drug until the date of death due to any cause. For a subject who is not known to have died by the end of study follow-up, OS

is censored at the date of last known alive date or at the analysis cutoff date, whichever is earlier. All dates which can support a subject's survival status (i.e., lab testing date, drug administration date) will be used to derive the last known alive date. Subjects with death or last known alive date after the analysis cutoff date will be censored at the cutoff date.

OS (in months) will be calculated as:

[(Date of death or censoring) – (Date of first dose of study drug) + 1] / 30.4375

The primary analysis population for OS is FAS.

5.2.5 Derivation of Best Overall Response and Sum of Diameters

Best overall response and sum of diameters (SOD) will be derived per RECIST Version 1.1 for the purpose of analyzing response related endpoints, e.g., ORR, DOR, DCR.

5.2.5.1 Best Overall Response

BOR is determined based on all available timepoint tumor response data for a subject. Responses recorded after new anticancer therapy or PD will be excluded from BOR derivation.

BOR with Confirmation

Confirmation of CR or PR should occur at the subsequent assessment no less than 4 weeks following the initial assessment at which CR or PR is observed. BOR with confirmation 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 at least 28 days apart, then the BOR for this subject is confirmed CR.
- If a subject has PR and another CR/PR at least 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 one tumor assessment record of CR/PR/SD which is at least 49 days after the first dose, then BOR is defined as SD.
- For subjects who do not have confirmed CR, confirmed PR, or SD, as defined above, but they have a tumor assessment of PD, their BOR is PD.
- Otherwise, BOR is defined as Not Evaluable (NE). For subjects without any postbaseline tumor assessment, BOR is defined as No Data (ND) which is a subcategory of NE.

BOR Regardless of Confirmation

The BOR regardless of confirmation for a subject is defined at the best timepoint tumor response in the order of CR, PR, SD, PD and NE. SD must be documented as present at least once at or after 49 days post first dose for BOR to be SD.

5.2.5.2 Sum of Diameters

Per RECIST Version 1.1, tumor burden is measured by the SOD of all target lesions (longest diameter for non-nodal lesions, short axis for nodal lesions) at each tumor assessment.

5.3 Exploratory Endpoints

5.3.1 Time to Response per Investigator Assessment

Time to response (TTR) per RECIST Version 1.1 by investigator assessment will be calculated as the time from the first dose of study drug to the first documented objective response (CR or PR that is subsequently confirmed) per investigator assessment. TTR will only be calculated for subjects who achieved a confirmed CR or PR per investigator assessment. The primary analysis population for DCR is RES who achieved a confirmed CR or PR.

5.3.2 Response Related Endpoints per RECIST Version 1.1 by Blinded Independent Central Review

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 or PR) 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. The following response related endpoints will be derived similarly as the corresponding endpoint per investigator assessment, except that timepoint tumor response per independent central review will be used.

- Confirmed ORR per BICR
- DOR per BICR
- DCR per BICR
- PFS per BICR
- BOR per BICR
- TTR per BICR

5.3.3 iRECIST Efficacy Endpoints by Investigator Assessment

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

5.3.3.1 Best Overall Response per iRECIST (iBOR)

iBOR is determined based on all available timepoint tumor response data for a participant. Participants will be classified by best response on study in order of iCR, iPR, iSD, iUPD, iCPD, and NE as outlined in iRECIST criteria. For best overall response of iSD, iSD must be documented as present at least 7 weeks after first dose. For confirmed iCR or iPR, response must be confirmed at a subsequent timepoint that is at least 4 weeks from the first documentation of iCR or iPR. Confirmatory scan for iUPD must occur at least 4 weeks after the date that iUPD was first observed but no longer than 8 weeks.

5.3.3.2 iORR

iORR with confirmed response is defined as the proportion of participants whose iBOR is a confirmed iCR or confirmed iPR per iRECIST as assessed by investigator. Definition of iBOR is specified in Section 5.3.3.1.

5.3.3.3 iDCR

iDCR with confirmed response is defined as the proportion of participants whose iBOR is a confirmed iCR or confirmed iPR or iSD per iRECIST as assessed by investigator. Definition of iBOR is specified in Section 5.3.3.1.

5.3.3.4 iPFS

iPFS is defined as the time from the start of study treatment to the first iUPD which is subsequently confirmed per iRECIST (iCPD) as assessed by investigator or death due to any cause whichever comes first.

Table 1 iPFS Definition

Situation	Date of Event or Censor	Outcome
No evaluable post-baseline imaging assessments, no death	Date of first dose (Day 1)	Censor
Death before first documented iUPD and subsequent anticancer therapy and not after two or more consecutive missed assessments	Date of death	Event
Documented iCPD (confirmed progression) before subsequent anticancer therapy and not after two or more consecutive missed assessments	Date of the initial iUPD that is subsequently confirmed	Event
Documented iUPD and the subject is not clinically stable to continue on treatment	Date of iUPD	Event
Documented iUPD without subsequent scans before subsequent anticancer therapy and the subject is no longer in response follow-up	Date of iUPD	Event
Documented iUPD and all subsequent assessments are iUPD(s) or NE(s) and the subject is no longer in response follow-up	Date of iUPD	Event
None of the above and subsequent anticancer therapy started	Date of last disease assessment prior to start of subsequent anticancer therapy	Censor
Death or documented iUPD right after two or more consecutive missed disease assessments	Date of last disease assessment prior to the missed visits	Censor
None of the above	Date of last disease assessment on study	Censor

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

New anti-cancer therapy includes therapies captured on new anti-cancer therapy eCRF and new radiation therapy eCRF.

For a participant who is censored, the last evaluable radiological tumor assessment refers to the participant's last radiological tumor assessment where the response is not NE.

When a cutoff date is applied to iPFS analysis, tumor assessment, death and new anti-cancer treatment occurring after the cutoff date will be excluded from the analysis.

5.3.3.5 iDOR

iDOR is defined as the time from the date of first documented response (iCR or iPR that is subsequently confirmed) as assessed by investigator to the date of first documented radiological disease progression per iRECIST or death due to any cause whichever occurs

first. iDOR will only be calculated for subjects achieving a confirmed iCR or iPR. The same censoring rules as described in Table 1 for iPFS will be applied for iDOR.

5.3.4 Biomarkers

Nectin-4 expression in tissue will be assessed by IHC H-score.

PD-L1 expression in tissue will be assessed by IHC combined positive score (CPS) for HR+/HER2- breast cancer (Cohort 1), TNBC (Cohort 2), head and neck cancer (Cohort 5), gastric adenocarcinoma or esophageal adenocarcinoma or GEJ adenocarcinoma (Cohort 7), esophageal squamous cell carcinoma (ESCC) (Cohort 8) and first-line head and neck squamous cell carcinoma (Cohort 9). PD-L1 expression in tissue will be assessed by IHC Tumor Proportion Score (TPS) for squamous or non-squamous non-small cell lung cancer (Cohorts 3 and 4).

Additional biomarkers may be evaluated to explore effects on anti-tumor activity and safety of the study drug and will be described in a separate biomarker analysis plan.

5.3.5 Pharmacokinetic Endpoints

To assess the pharmacokinetics of enfortumab vedotin and monomethyl auristatin E (MMAE), the following pharmacokinetic endpoints will be evaluated:

- Plasma concentration of MMAE
- Serum concentration of enfortumab vedotin

5.3.6 Incidence of Antitherapeutic Antibodies

The incidence of ATA formation to the enfortumab vedotin will be evaluated.

5.3.7 Patient Reported Outcome

5.3.7.1 Cohorts 1 to 8

To evaluate the treatment effect of enfortumab vedotin on quality of life, PRO per Euro quality of life - 5 dimensions (EQ-5D-5L) and global pain assessment (worst pain in the last 24 hours) will be assessed.

- EQ-5D-5L

  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). This questionnaire also records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analogue scale (VAS) [Herdman, 2011].

A unique EQ-5D-5L health state is defined by combining 1 level from each of the 5 dimensions: this defines a profile that is primarily reported as 5-digit number, for instance 11221. A total of 3125 possible health states are defined in this way. For example, state 11111 indicates no problems on any of the 5 dimensions, while 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression. The instrument was specifically designed to provide an overall single number, called weighted index or utility index, for each of the health states resulting from the combination of item response [Dolan, 1997]. The utility index can be only derived from patients who have provided a complete 5-response profile. A higher index indicates better QoL. The EQ-5D-5L utility index value will be derived using the value set for England [Devlin, 2012]. The algorithm to calculate the utility index using England value set is presented in Appendix 9.3.

The analysis population is FAS.

- Global pain assessment

  Global pain assessment is a subject's rating of his/her pain on a 0 to 10 scale that best describes the pain at its worst in the last 24 hours. Refer to Protocol Appendix 12.11 for a sample questionnaire.

  The analysis population is FAS.

PRO completion status at each visit will be reported for each instrument:

- Completion rate at each visit will be calculated as the number of subjects with at least one question completed divided by the number of subjects in the FAS population
- Compliance rate at each visit will be calculated for subjects who are expected to have PRO assessment at the visit. The following will be provided:
  - The number and percentage of subjects with at least one questions completed
  - The number and percentage of subjects with all questions completed (for EQ-5D-5L only)
  - The number and percentage of subjects with either utility index calculated or VAS completed (for EQ-5D-5L only)

5.3.7.2 Cohort 9

- EORTC QLQ H&N43

  The EORTC QLQ H&N43 contains 43 items of 12 multi-item and 7 single-item symptom subscales namely pain in the mouth, swallowing, problems with teeth, dry mouth and sticky saliva, problems with senses, speech, body image, social eating, sexuality, problems with shoulder, skin problems, fear of progression, problems opening mouth, coughing, social contact, swelling in the neck, weight loss, problems with wound healing, neurological problems. Patients report the extent to which they have experienced these symptoms or problems during the past week. The scores are

from 1 to 4 (0 - not at all; 1 - A little; 2 - Quite a bit; 4 - very much). Refer to Protocol Appendix 12.13 for a sample questionnaire. The analysis population is FAS.

- Global Pain Assessment

  Global pain assessment is a subject's rating of his/her pain on a 0 to 10 scale that best describes the pain at its worst in the last 24 hours. Refer to Protocol Appendix 12.11 for a sample questionnaire. The analysis population is FAS.

- PRO-CTCAE

  Three questions will be utilized from the PRO-CTCAE to obtain subject assessment of fatigue and diarrhea symptoms. Patients report the frequency, severity and interference of the symptoms in the past 7days. The diarrhea frequency question comprises 5 levels from Never to Almost constantly. The fatigue severity question comprises 5 levels from None to Very severe. The fatigue interference question comprises 5 levels from Not at all to Very much. Refer to Protocol Appendix 12.14 for a sample questionnaire. The analysis population is FAS.

- 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). Refer to Protocol Appendix 12.15 for a sample questionnaire. The analysis population is FAS.

PRO completion status at each visit will be reported for each instrument:

- Completion rate at each visit will be calculated as the number of subjects with at least one question completed divided by the number of subjects in the FAS population
- Compliance rate at each visit will be calculated for subjects who are expected to have PRO assessment at the visit. The following will be provided:
  - The number and percentage of subjects with at least one questions completed
  - The number and percentage of subjects with all questions completed (for EORTC QLQ H&N43 and PRO-CTCAE only)

5.4 Safety Endpoints

Safety endpoints including adverse events (AEs), laboratory test, vital signs, 12-lead electrocardiogram (ECGs) and Eastern Cooperative Oncology Group (ECOG) performance status are secondary endpoints of the study.

Safety will be assessed by evaluation of the following variables:

- Treatment-emergent adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).
    - TEAE is defined as an adverse event observed after starting administration of the study drug and within 30 days after taking the last dose of study drug. For serious AEs in Cohort 9, TEAE definition is revised to within 90 days after the last dose of either study drug. If the adverse event occurs on the first dose date and the onset check box is marked "Onset after first study drug taken" or the onset check box is left blank, then the adverse event will be considered treatment emergent. If the adverse event occurs on the first dose date and the onset check box is marked "Onset before first study drug taken", then the adverse event will not be considered treatment emergent. If a subject experiences an event both during the pre-investigational period and during the investigational period, the event will be considered as TEAE only if it has worsened in severity (i.e., it is reported with a new start date). If a complete onset date is unknown, and the onset check box is marked "Onset after first study drug taken", then the adverse events will be considered treatment emergent. If the onset check box is marked "Onset before study drug taken", then the adverse event will not be considered treatment emergent. If onset check box is left blank, imputed onset date as specified in Section 6.9.2 will be used to determine whether an adverse event is treatment emergent.
    - A drug-related TEAE is defined as any TEAE with relationship to study drug (enfortumab vedotin or pembrolizumab) marked as "Yes" on eCRF as assessed by investigators or with missing assessment of the causal relationship.
- Serious adverse events (SAEs) include adverse events that are flagged as serious by the investigator on eCRF, or with missing serious assessment on eCRF, or upgraded by the Sponsor based on review of the Sponsor's list of Always Serious term or the important medical event process.
- Adverse events of special interest for enfortumab vedotin (AESI)
    - For cohorts 1 to 9, hyperglycemia, peripheral neuropathy, dry eye, corneal disorders and blurred vision, skin reactions, and infusion related reactions are considered adverse events of special interest (AESI) for enfortumab vedotin. These are medical concepts of composite terms based on the search criteria utilizing MedDRA terminology (standard MedDRA query [SMQ], sponsor specific query [SSQ], customized MedDRA query [CMQ], high level group term [HLGT], high level term [HLT], preferred term [PT]). Other AEs may be added as AESI as necessary due to ongoing pharmacovigilance activities. The search criteria for AESI will be maintained in a separate document and finalized prior to database lock.
    - For selected AESI, time to onset of AESI will be calculated.
      Time to first onset of a specific AESI will be calculated as the time from the first dose of study drug to the onset of the first treatment-emergent adverse event that meets the respective search criteria.

- For selected AESI, time to resolution of AESI will be calculated. Resolution is defined as event outcome of 'recovered/resolved' or 'recovered/resolved with sequelae'. For treatment-emergent events with an outcome of 'recovered/resolved' or 'recovered/resolved with sequelae', time to resolution will be calculated as time from the event onset date to end date.

  Time to resolution is defined at the event level. AE records that belong to the same event will be linked.

- Other AEs of risk for enfortumab vedotin
  For cohorts 1 to 9, pneumonitis/interstitial lung disease (ILD) is defined as other AEs of risk for EV. Similar as AESI, terms are based on the search criteria utilizing MedDRA terminology.
- Adverse events of special interest for pembrolizumab (AEOSI)
  - For cohort 9, AEOSI are immune-mediated events and infusion-related reactions, following the Keytruda AEOSI List which is a pre-specified list of preferred terms (PTs) developed by MSD to consistently characterize the nature and frequency of each AEOSI across the clinical program, regardless of causality as reported by investigators. These PTs are considered to be medically equivalent to the identified risks for pembrolizumab. The list of PTs may be updated by MSD based on emerging pembrolizumab safety data or as a result of MedDRA updates.
- Clinical laboratory variables

Below is a table of the laboratory tests that will be performed during the conduct of the study.

Panel/Assessments	**Parameters to be Analyzed**	**NCI-CTCAE Grading (Hyper/Hypo)**
Hematology	Hematocrit (Hct) Hemoglobin (Hb) Platelets Red blood cell count (RBC) White blood cell count (WBC) White blood cell count differential • Absolute neutrophils count (ANC) • Eosinophils • Basophils • Lymphocytes • Monocytes	N/A Both Hypo N/A Both Hypo N/A N/A Both N/A
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)	Hypo Hyper Hyper Hyper N/A Hyper N/A Both N/A Hyper Both N/A N/A Both Hypo Both Both N/A Hyper Hyper N/A N/A Hyper
Thyroid Function Tests (Cohort 9 only)	Triiodothyronine (T3) or Free Triiodothyronine (FT3) Free thyroxine (FT4) Thyroid stimulating hormone (TSH)	N/A N/A N/A
Coagulation (Cohort 9 only)	INR PT PTT	Hyper N/A Hyper
Pregnancy Test	Serum or urine β-human Chorionic Gonadotropin (hCG).	N/A

- Vital signs (systolic and diastolic blood pressure (mmHg), pulse rate (beats/minute), and body temperature (ºC))
- 12-lead electrocardiogram (ECG)
- ECOG performance scores

5.5 Other Endpoints

5.5.1 Cohorts 1 to 8

- Duration of exposure (months)

  Duration of exposure = [min (last date of exposure, death, cutoff date) – first dose date +1] / 30.4375

  Last date of exposure = (initial dose date of the last cycle + 28 -1)

- Number of cycles

  Total number of cycles with non-zero dosing

- Cumulative dose (mg)

  Sum of (total dose administered) across all days

  Total dose administered on a dosing day (mg) = final concentration (mg/mL) * actual volume administered (mL)

- Planned dose intensity (mg/kg/cycle)

  Initial dose of enfortumab vedotin multiplied by planned number of dosing days per cycle.

  For example, subject is planned to receive enfortumab vedotin at a dose of 1.25mg/kg on days 1, 8, 15 of each cycle, the planned dose intensity = 1.25mg/kg * 3 = 3.75 mg/kg per cycle.

- Dose intensity (mg/kg/cycle)

$$\frac{\sum_{i=1}^{NC}\sum_{j=1}^{3}(TD_{i,j}/W_{i,j})}{(last\ date\ of\ exposure - first\ dose\ date + 1)/28}$$

  where, $TD_{i,j}$ is the actual total drug administered at cycle i day j,

  $W_{i,j}$ is the body weight recorded at cycle i day j,

  NC is the number of cycles with non-zero dosing.

  If body weight >100 kg, then $W_{i,j}$ = 100 kg. If there is no dose administered on a planned dosing day in a cycle, then $TD_{i,j}$ = 0 mg.

- Relative dose intensity (%)

$$\frac{Dose\ intensity}{Planned\ dose\ intensity} \times 100$$

5.5.2 Cohort 9

For enfortumab vedotin:

- Duration of exposure (months)

  Duration of exposure = [min (last date of exposure, death, cutoff date) – first dose date +1] / 30.4375

  Last date of exposure = (initial dose date of the last cycle + 21 -1)

- Number of cycles

  Total number of cycles with non-zero dosing

- Cumulative dose (mg)

  Sum of (total dose administered) across all days

  Total dose administered on a dosing day (mg) = final concentration (mg/mL) * actual volume administered (mL)

- Planned dose intensity (mg/kg/cycle)

  Initial dose of enfortumab vedotin multiplied by planned number of dosing days per cycle.

  For example, subject is planned to receive enfortumab vedotin at a dose of 1.25mg/kg on days 1, 8 of each cycle, the planned dose intensity = 1.25mg/kg * 2 = 2.5 mg/kg per cycle.

- Dose intensity (mg/kg/cycle)

$$\frac{\sum_{i=1}^{NC}\sum_{j=1}^{2}(TD_{i,j}/W_{i,j})}{(last\ date\ of\ exposure - first\ dose\ date + 1)/21}$$

  where, $TD_{i,j}$ is the actual total drug administered at cycle i day j,

  $W_{i,j}$ is the body weight recorded at cycle i day j,

  NC is the number of cycles with non-zero dosing.

  If body weight >100 kg, then $W_{i,j}$ = 100 kg. If there is no dose administered on a planned dosing day in a cycle, then $TD_{i,j}$ = 0 mg.

- Relative dose intensity (%)

$$\frac{Dose\ intensity}{Planned\ dose\ intensity} \times 100$$

For pembrolizumab:

- Duration of exposure (months)

  Duration of exposure = [min (last date of exposure, death, cutoff date) – first dose date +1] / 30.4375

  Last date of exposure = (initial dose date of the last cycle + 21 -1)

- Number of cycles

  Total number of cycles with non-zero dosing

- Cumulative dose (mg)

  Sum of (total dose administered) across all days

5.5.3 All cohorts

- Previous and concomitant medication

  Previous medication is defined as medication with at least one dose taken before the date of the first dose of study drug (exclusive).

  Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose plus 30 days (inclusive) of study drug.

- Previous and concomitant non-medication therapy

  Previous non-medication therapy is defined as non-medication therapy administered at least once before the date of the first dose of study drug (exclusive).

  Concomitant non-medication therapy is defined as non-medication therapy administered at least once between the date of first dose (inclusive) and the date of last dose plus 30 days (inclusive) of study drug.

- Ophthalmologic assessment (visual acuity measurement, slit lamp biomicroscopy, tonometry and dilated fundus examination)

6 STATISTICAL METHODOLOGY

6.1 General Considerations

Continuous data will be summarized descriptively including the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. When needed, the use of other percentiles (e.g., 10%, 25%, 75%, 90%) will be specified in the relevant section. In addition, for plasma (MMAE) and serum concentrations, the coefficient of variation, the geometric mean and the coefficient of variation for geometric mean will also be calculated. Categorical data will be summarized by frequencies and percentages. Percentages by categories will be based on the number of subjects with no missing data, i.e., the percentages for the nonmissing categories will add up to 100%.

Unless otherwise specified, confidence intervals (CIs) will be calculated at two-sided 95% level. For time-to-event endpoints, median survival time will be estimated using Kaplan-Meier method, with 2-sided 95% CI.

Baseline value is defined as the last nonmissing measurement prior to the first dose of study drug unless specified otherwise. In general, data will be summarized by cohort and overall.

All data summarization and analyses will be performed using SAS® Version 9.4 or higher on Red Hat Enterprise Linux. Specifications for table, figures, and data listing formats can be found in the TLF specifications.

6.2 Study Population

6.2.1 Disposition of Subjects

The following subject data will be presented:

- Number and percentage of subjects with informed consent, discontinued before enrollment, and enrolled will be summarized for all subjects with informed consent for overall only;
- Number and percentage of subjects included in each analysis set will be summarized by cohort and overall for all enrolled subjects;
- Number and percentage of subjects discontinued treatment, and the primary reason for treatment discontinuation will be summarized by cohort and overall for FAS;
- Number and percentage of subjects completed or discontinued 30-day safety follow-up, and the primary safety follow-up status will be summarized by cohort and overall for FAS;
- Number and percentage of subjects discontinued post treatment follow-up, and the primary post treatment follow-up status will be summarized by cohort and overall for FAS;
- Number and percentage of subjects discontinued long-term follow-up and the primary long-term follow-up status will be summarized by cohort and overall for FAS; and
- Number and percentage of subjects completed or discontinued the screening period and the primary screening status will be summarized for all subjects with informed consent for overall only.

6.2.2 Protocol Deviations

Protocol deviations as defined in the study protocol [Section 10.3 Major Protocol Deviations] will be assessed for all enrolled subjects. The number and percentage of subjects with the following protocol deviation criteria will be summarized for each criterion and overall, by cohort and overall as well as by investigative site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Subjects with more than one protocol deviation will be counted once for the overall summary. A data listing will be provided by site and subject. The protocol deviation criteria will be uniquely identified in the summary table and listing.

The unique identifiers will be as follows:

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

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

PD3 - Received wrong treatment or incorrect dose. For enfortumab vedotin, incorrect dose will be defined as less than or greater than 10% from the intended dose, i.e., less

than 90% of the intended dose or greater than 110% of the intended dose. For pembrolizumab, any dose of 1000 mg or greater will be considered incorrect dose.

PD4 - Received excluded concomitant treatment.

6.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized descriptively by cohort and overall for FAS and RES.

Demographic characteristics:

- Age, Age categories (< 65 years, ≥ 65 to < 75 years, ≥ 75 years), EudraCT age categories (≥ 18 to ≤ 64 years, ≥ 65 to ≤ 84 years, ≥ 85 years)
- Sex
- Ethnicity
- Race
- Region (North America, Asia)
- Baseline Height
- Baseline weight, baseline weight groups (≤ 100 kg, > 100 kg)
- Baseline BMI, baseline BMI categories (< 18.5, ≥ 18.5 to < 25, ≥ 25 to < 30, ≥ 30)

Baseline characteristics:

- Baseline measurable disease (Yes, No)
- Nectin-4 IHC H-score (including 25th percentile and 75th percentile)
- Baseline PD-L1 IHC status (PD-L1 low, PD-L1 high as defined in Table 2)
- ECOG PS (0, 1, > 1)
- Hemoglobin, Hemoglobin categories (< 10 g/dL, ≥ 10 g/dL)
- Albumin, Albumin categories (< LLN, ≥ LLN)
- HbA1C, HbA1C categories (≤5.6%, 5.7 to < 6.5%, ≥ 6.5%)
- Fasting glucose, fasting glucose CTCAE grade
- Total cholesterol, total cholesterol categories (low, normal, high)
- Baseline hepatic function group

  Baseline hepatic function group is defined per the NCI-ODWG criteria based on total bilirubin and AST at the baseline as follows:

  Normal: total bilirubin ≤ ULN and AST ≤ ULN
  Mild dysfunction: (ULN < total bilirubin ≤ 1.5×ULN) or
  (AST > ULN and total bilirubin ≤ ULN)
  Moderate dysfunction: 1.5×ULN < total bilirubin ≤ 3×ULN
  Severe dysfunction: total bilirubin > 3×ULN

- Baseline renal function group

  Baseline renal function group is defined based on estimated creatinine clearance (CrCl) by Cockcroft-Gault formula.

  Normal: ≥ 90 mL/min

Mild insufficiency: ≥ 60 to < 90 mL/min
Moderate insufficiency: ≥ 30 to < 60 mL/min
Severe insufficiency: ≥15 to < 30 mL/min
End stage renal disease: < 15 mL/min

Cockcroft-Gault formula for estimating CrCl (mL/min):

$$\frac{[140 - age(years)] \times body\ weight\ (kg) \times (0.85\ if\ female)}{serum\ creatinine\ (mg/dL) \times 72}$$

- Baseline tobacco use
  - Prior tobacco history (never used, former smoker, current smoker, unknown)
  - Number of pack-years for current or former smoker
- History of diabetes/hyperglycemia defined as any hyperglycemia SSQ/CMQ

Disease specific history will be summarized descriptively by cohort and overall for FAS and RES.

- Time (months) since initial diagnosis of primary cancer
- (first dose date – date of initial diagnosis of primary cancer + 1)/30.4375
- Primary cancer type and location (location will be summarized for breast cancer, head and neck cancer and HNSCC only)
- Histological type at diagnosis
- Anatomic staging at screening
- Prior PD-L1 testing: Yes/No and test results
- Disease specific biomarkers:
  - For HR+/HER2- breast cancer (Cohort 1) and TNBC (Cohort 2): HER2 status and test method, ER status, PgR status, PIK3CA mutation status, BRCA mutation status
  - For squamous NSCLC (Cohort 3) and non-squamous NSCLC (Cohort 4): ALK rearrangement status and test method, EGFR status and test method, BRAF mutation status, NTRK fusion status, ROSI rearrangement status
  - For head and neck cancer and HNSCC: HPV status
  - For gastric or GEJ or esophageal cancer (Cohorts 6, 7, 8): HER2 status and test method, MSI status and test method, MMR status
- Brain metastases

Medical history other than primary cancer type and conditions existing at baseline will be coded in MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone, by cohort and overall for FAS and other analysis populations if necessary. Baseline conditions are defined as those ongoing at the time of informed consent or arise following the time of informed consent and before the first dose of study drug. For ongoing medical conditions, Common Terminology Criteria for Adverse Events (CTCAE) grade will be provided in listing.

Number and percentage of subjects enrolled in each country and investigator site will also be presented.

6.2.4 Prior Systemic Anti-Cancer Therapy (for cohorts 1 to 8 only)

Prior systemic anti-cancer therapy will be summarized descriptively by cohort and overall for FAS and RES.

- Prior lines of systemic therapy (1 line, 2 lines, ≥ 3 lines)
- Prior lines of systemic therapy in metastatic setting (1 line, 2 lines, ≥ 3 lines)
- Type of prior systemic therapy (e.g., PD-L1/PD-1 inhibitor, platinum-based treatment, taxane, fluoropyrimidine containing therapy, targeted therapy, cetuximab, anthracycline, alkylating agent, hormonal therapy, PARP inhibitor, CDK 4/6 inhibitor) and subtype if applicable
- Setting of prior systemic therapy
- Setting of the most recent prior systemic therapy
- Relapse status (yes vs. no)
    - within 6 months after completion of cytotoxic therapy in neoadjuvant or adjuvant setting for HR+/HER2- breast cancer (Cohort 1), TNBC (cohort 2), and gastric or GEJ or esophageal cancer (Cohorts 6, 7, 8)
    - within 6 months after completion of platinum-based therapy in neoadjuvant or adjuvant setting for squamous NSCLC (Cohort 3), non-squamous NSCLC (Cohort 4), and head and neck cancer (Cohort 5)
- Best response to prior systemic therapy
- Best response to the most recent prior systemic therapy
- Reason for discontinuing the most recent prior systemic therapy
- Time since completion/discontinuation of the most recent prior systemic therapy

Setting of prior systemic therapy, best response to prior systemic therapy, reason for discontinuation, and time since completion/discontinuation of prior systemic therapy may be summarized by type of prior systemic therapy.

6.2.5 Prior Radiation Therapy

Number and percentage of subjects who previously received any radiation therapy for the treatment of primary cancer, area radiated, and reason for radiation therapy will be summarized by cohort and overall for FAS and RES.

6.2.6 Prior Procedures for Primary Cancer and Concomitant Procedures

Number and percentage of subjects who had previously undergone any surgery or procedures for the treatment of primary cancer will be summarized by cohort and overall for FAS and RES.

Number and percentage of subjects who had undergone any on-study surgery or procedures will be summarized by cohort and overall for FAS and RES.

6.2.7 Previous and Concomitant Medications

Previous medications will be summarized by therapeutic subgroup (ATC 2nd level), chemical subgroup (ATC 4th level) and preferred WHO name by cohort and overall for the SAF.

As with previous medication, concomitant medications will be summarized by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name by cohort and overall for the SAF. Subjects taking the same medication multiple times will be counted once per medication and investigational period. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups. All previous and concomitant medications will be coded by indication-specific ATC.

6.2.8 Previous and Concomitant Non-Medication Therapy

Subjects with previous and concomitant non-medication therapy and its reason for use will be provided in the listing.

6.2.9 New Anti-Cancer Therapy

Number and percentage of subjects receive any new anti-cancer therapy will be presented. Types of anti-cancer therapy and the reason for starting the new anti-cancer therapy will be summarized by cohort and overall for SAF.

6.2.10 New Radiation Therapy

Number and percentage of subjects who receive any subsequent radiation therapy will be presented. Types of radiation therapy and the reason for starting the new radiation therapy will be summarized by cohort and overall for SAF.

6.3 Study Drugs Exposure and Compliance

6.3.1 Cohorts 1 to 8

The following information of drug exposure will be presented by cohort and overall for the SAF:

- Descriptive statistics for duration of exposure, number of cycles, cumulative dose, planned dose intensity, dose intensity and relative dose intensity.
- Number and percentage of subjects with dose adjustment and reason for dose adjustment, dose reduction, and dose interruption. Dose reduction is defined as a dose given on a planned dosing day that is lower than the subject's initial dose of enfortumab vedotin. Dose interruption is defined as zero dose given on a planned dosing day with dosing resumed later.
- Duration of exposures will also be categorized according to the following categories, number and percentage of subjects in each categories will be summarized.
    - < 1 month
    - ≥ 1 and < 3 months
    - ≥ 3 and < 6 months
    - ≥ 6 months
    - Unknown

6.3.2 Cohort 9

The exposure analysis will be summarized by enfortumab vedotin, pembrolizumab and any drug for the SAF.

- Enfortumab vedotin: descriptive statistics for duration of exposure, number of cycles, cumulative dose, planned dose intensity, dose intensity and relative dose intensity. Number and percentage of subjects with dose adjustment and reason for dose adjustment, dose reduction, and dose interruption.
- Pembrolizumab: descriptive statistics for duration of exposure, number of cycles and cumulative dose. Number and percentage of subjects with dose interruption and reason for dose interruption.
- Any drug: descriptive statistics for duration of exposure and number of cycles
- Duration of exposures for enfortumab vedotin, pembrolizumab and any drug will also be categorized according to the following categories, number and percentage of subjects in each categories will be summarized.
    - < 1 month
    - ≥ 1 and < 3 months
    - ≥ 3 and < 6 months
    - ≥ 6 months and < 12 months
    - ≥ 12 months
    - Unknown

6.4 Analysis of Efficacy

Efficacy analysis will be conducted on the RES and FAS. RES will be the primary analysis population for response related endpoint, FAS will be the primary analysis population for PFS and OS.

6.4.1 Analysis of Primary Efficacy Endpoint

6.4.1.1 Primary Analysis for Primary Efficacy Endpoint

Confirmed ORR per RECIST Version 1.1 by investigator assessment will be calculated for each cohort. The corresponding 95% confidence interval will be constructed using the Clopper-Person method. The primary analysis set for confirmed ORR is the RES per investigator assessment.

ORR based on BOR regardless of the confirmation will also be calculated to evaluate the impact on ORR due to missing of confirmatory scans or PD after the initial response.

6.4.2 Analysis of Secondary Efficacy Endpoints

6.4.2.1 DOR per Investigator Assessment

DOR per RECIST Version 1.1 by investigator assessment will be summarized for subjects with confirmed CR or PR per investigator assessment in RES. Number and percentage of subjects with event and each event type (death, PD), censoring and each censoring type (no event, start new anti-cancer treatment before PD or death) will be summarized. DOR will be

analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median, first quartile, third quartile and the corresponding two-sided 95% CIs will be calculated. The DOR rate at months 6, 12, 24, 36 will be summarized along with the corresponding 95% CI if applicable.

6.4.2.2 DCR per Investigator Assessment

DCR per RECIST Version 1.1 by investigator assessment will be calculated for each cohort. The corresponding 95% confidence interval will be constructed using the Clopper-Person method. The primary analysis set for DCR is the RES per investigator assessment.

DCR based on BOR regardless of the confirmation will also be calculated to evaluate the impact on DCR due to missing of confirmatory scans or PD after initial response.

6.4.2.3 PFS per Investigator Assessment

PFS per RECIST Version 1.1 by investigator assessment will be summarized for each cohort in the FAS. Number and percentage of subjects with an event and each event type (death, PD), censoring and each censoring type (no event, start new anti-cancer treatment before PD or death) will be summarized. PFS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median, first quartile, third quartile and the corresponding two-sided 95% CIs will be calculated. The PFS rate at months 6, 12, 24 and 36 will be summarized along with the corresponding 95% CI if applicable.

6.4.2.4 OS

OS will be summarized for each cohort in the FAS. Number of subjects with event and censoring will be summarized. OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median, first quartile, third quartile and the corresponding two-sided 95% CIs will be calculated. The OS rate at months 6, 12, 24, 36 will be summarized along with the corresponding 95% CI if applicable.

6.4.2.5 BOR per Investigator Assessment

BOR with confirmation per RECIST Version 1.1 by investigator assessment will be summarized by cohort in RES. The number and percentage of subjects in each category will be presented.

BOR regardless of confirmation per RECIST Version 1.1 by investigator assessment will be summarized in the same way.

6.4.2.6 SOD

The maximum percent reduction in SOD from baseline per RECIST Version 1.1 by investigator assessment will be summarized using descriptive statistics by responder (confirmed CR or PR), SD and PD for each cohort. Maximum percent reduction in SOD from baseline will also be presented graphically in waterfall plot.

6.4.3 Analysis of Exploratory Endpoints

6.4.3.1 TTR per Investigator Assessment

TTR per investigator will be summarized with descriptive statistics by cohort for subjects achieving a confirmed CR or PR per RECIST Version 1.1 by investigator assessment in RES.

6.4.3.2 Endpoints per RECIST Version 1.1 by BICR

For cohorts with imaging scans read by BICR as defined in Section 5.3.2, confirmed ORR per BICR, DOR per BICR, DCR per BICR, PFS per BICR, BOR per BICR and TTR per BICR will be analyzed in the same way as the corresponding endpoints per investigator assessment as described in Sections 6.4.1 and 6.4.2.

Analyses based on RES population will require subjects to have measurable disease at baseline per BICR.

6.4.3.3 Endpoints per iRECIST by Investigator Assessment

For cohort 9 as defined in Section 5.3.3, confirmed iORR, iDOR, iDCR and iPFS per iRECIST as assessed by investigator will be analyzed in the same way as the corresponding endpoints per investigator assessment as described in Sections 6.4.1 and 6.4.2.

6.4.3.4 Biomarkers

For each cohort, baseline Nectin-4 IHC H-score will be summarized using mean, standard deviation, minimum, maximum, median, 25th percentile and 75th percentile. An exploratory analysis of assessing baseline IHC H-score with clinical outcomes may be conducted.

For each cohort, baseline PD-L1 results will be summarized by PD-L1 low and PD-L1 high according to the categories listed in the table below:

Table 2 PD-L1 Categorization for Each Cohort

Cohort	Cancer Type	PD-L1 Low	PD-L1 High
1	HR+/HER2- breast cancer	CPS < 1	CPS ≥ 1
2	TNBC	CPS < 10	CPS ≥ 10
3	Squamous NSCLC	TPS < 1%	TPS ≥ 1%
4	Non-squamous NSCLC	TPS < 1%	TPS ≥ 1%
5	Head and neck cancer	CPS < 1	CPS ≥ 1
7	Gastric adenocarcinoma or EAC or GEJ adenocarcinoma	CPS < 1	CPS ≥ 1
8	ESCC	CPS < 10	CPS ≥ 10
9	HNSCC	CPS < 1	CPS ≥ 1

An exploratory assessment of PD-L1 CPS or TPS with clinical outcomes may be conducted.

Summary statistics and exploratory assessments of Nectin-4 or PD-L1 expression with clinical outcome for combined cohorts may be performed and will be described in a separate biomarker analysis plan.

Additional biomarkers may be evaluated to explore effects on anti-tumor activity and safety of the study drug and will be described in a separate biomarker analysis plan.

6.4.3.5 Incidence of Antitherapeutic Antibodies

The number and percentage of subjects with positive postbaseline ATA will be tabulated by baseline ATA status for each cohort and overall for FAS.

6.4.3.6 EQ-5D-5L (for cohorts 1 to 8 only)

EQ-5D-5L will be summarized at each visit by cohort and overall for the FAS. Number and percentage of subjects in each level of 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) will be presented. A stacked column chart of the distribution of response to each dimension will be presented by visit, cohort and overall for FAS.

EQ-5D-5L utility index score and VAS will be summarized at each visit by cohort and overall for the FAS using descriptive statistics (mean, standard deviation, minimum, maximum and median). Additionally, a within-subject change will be calculated as the postbaseline score minus the baseline score and summarized in the same way.

The completion rate and compliance rate of EQ-5D-5L will be summarized at each visit by cohort and overall.

6.4.3.7 Global Pain Assessment

Global pain assessment score will be summarized at each visit by cohort and overall for the FAS using descriptive statistics. Additionally, a within-subject change will be calculated as the postbaseline score minus the baseline score and summarized in the same way. A line graph of median score together with 25^{th} percentile and 75^{th} percentile over time will be produced by cohort and overall.

The completion rate and compliance rate of global pain assessment will be summarized at each visit by cohort and overall.

6.4.3.8 EORTC QLQ H&N43 (for cohort 9 only)

The symptom scores will be summarized at each visit for the FAS using descriptive statistics (mean, standard deviation, minimum, maximum and median). Additionally, a within-subject change will be calculated as the postbaseline score minus the baseline score and summarized in the same way. The scoring algorithm is described in Appendix 4.

The completion rate and compliance rate of EORTC QLQ H&N43 will be summarized at each visit.

6.4.3.9 PRO-CTCAE (for cohort 9 only)

The assessment of fatigue and diarrhea symptoms will be summarized at each visit for the FAS. Number and percentage of subjects in each level of 3 questions will be presented. A stacked column chart of the distribution of response to each question will be presented by visit for FAS.

The completion rate and compliance rate of PRO-CTCAE will be summarized at each visit.

6.4.3.10 FACT-G (for cohort 9 only)

The response of GP5 question will be summarized at each visit for the FAS. Number and percentage of subjects in each level (Not at all, A little bit, Somewhat, Quite a bit, Very much) will be presented. A stacked chart of the distribution of response will be presented by visit for FAS.

The completion rate and compliance rate of FACT-G will be summarized at each visit.

6.4.4 Subgroup Analysis for Efficacy Endpoints

Exploratory analysis for selected efficacy endpoints per RECIST Version 1.1 (e.g., ORR, DCR, PFS, OS) may be conducted on subgroups based on demographic and baseline characteristics, disease history, and prior anti-cancer therapy when sufficient data are available, including but not limited to age, sex, race, region, baseline ECOG PS, baseline hemoglobin, anatomic staging at baseline, prior lines of therapy, prior lines of therapy in metastatic setting, prior use of CPI treatment, prior use of platinum based treatment, prior use of taxane, prior use of fluoropyrimidine therapy, prior use of targeted therapy, best response to prior anti-cancer therapy, best response to selected subtype of prior anti-cancer therapy if applicable. For cohort 9, subgroup analysis may be also conducted based on PD-L1 central testing results and time since prior radiation therapy.

6.5 Analysis of Safety

All analysis of safety will be presented by cohort and overall for the SAF, unless specified otherwise.

6.5.1 Adverse Events

All adverse events recorded on treatment including within 30 days from the last study treatment, or within 90 days from the last study treatment for SAEs in Cohort 9 will be summarized.

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

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

The definition of TEAEs leading to treatment discontinuation, TEAEs leading to interruption of treatment and TEAEs leading to dose reduction is listed below. The rules will be followed in the applicable TEAE analyses.

- TEAEs leading to permanent discontinuation of study drug is defined as TEAEs leading to withdrawal of any study drug (enfortumab vedotin or pembrolizumab) in Cohorts 1-9. TEAEs leading to permanent discontinuation of enfortumab vedotin is defined as TEAEs leading to withdrawal of enfortumab vedotin in Cohort 9. TEAEs

leading to permanent discontinuation of pembrolizumab is defined as TEAEs leading to withdrawal of pembrolizumab in Cohort 9.

- TEAEs leading to dose interruption is defined as TEAEs leading to interruption of any study drug (enfortumab vedotin or pembrolizumab) in Cohorts 1-9. TEAEs leading to interruption of enfortumab vedotin is defined as TEAEs leading to interruption of enfortumab vedotin in Cohort 9. TEAEs leading to interruption of pembrolizumab is defined as TEAEs leading to interruption of pembrolizumab in Cohort 9.
- TEAEs leading to dose reduction is defined as TEAEs leading to reduction of enfortumab vedotin in Cohorts 1-9. Pembrolizumab reduction is not allowed.

An overview table to report the number and percentage of subjects and another overview table to report number of events and events adjusted by patient year of drug exposure will include the following details by cohort and overall:

- Number and percentage of subjects with TEAEs,
- Number and percentage of subjects with drug-related TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number and percentage of subjects with serious drug-related TEAEs,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of enfortumab vedotin,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of pembrolizumab,
- Number and percentage of subjects with drug-related TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with drug-related TEAEs leading to permanent discontinuation of enfortumab vedotin,
- Number and percentage of subjects with drug-related TEAEs leading to permanent discontinuation of pembrolizumab,
- Number and percentage of subjects with TEAEs leading to dose reduction,
- Number and percentage of subjects with drug-related TEAEs leading to dose reduction,
- Number and percentage of subjects with TEAEs leading to dose interruption,
- Number and percentage of subjects with TEAEs leading to interruption of enfortumab vedotin,
- Number and percentage of subjects with TEAEs leading to interruption of pembrolizumab,
- Number and percentage of subjects with drug-related TEAEs leading to dose interruption,
- Number and percentage of subjects with drug-related TEAEs leading to interruption of enfortumab vedotin,

- Number and percentage of subjects with drug-related TEAEs leading to interruption of pembrolizumab,
- Number and percentage of subjects with grade 3 or higher TEAEs,
- Number and percentage of subjects with grade 3 or higher drug-related TEAEs,
- Number and percentage of subjects with TEAEs leading to death,
- Number and percentage of subjects with drug-related TEAEs leading to death,
- Number and percentage of subjects with TEAEs leading to death excluding disease progression,
- Number and percentage of subjects with drug-related TEAEs leading to death excluding disease progression, and
- Number of deaths.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by cohort and overall. Summaries will be provided for the following:

- TEAEs
- drug related TEAEs,
- serious TEAEs,
- drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- TEAEs leading to permanent discontinuation of enfortumab vedotin,
- TEAEs leading to permanent discontinuation of pembrolizumab,
- drug related TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of enfortumab vedotin,
- drug related TEAEs leading to permanent discontinuation of pembrolizumab,
- TEAEs leading to dose reduction,
- drug-related TEAEs leading to dose reduction,
- TEAEs leading to dose interruption,
- TEAEs leading to interruption of enfortumab vedotin,
- TEAEs leading to interruption of pembrolizumab,
- drug-related TEAEs leading to dose interruption,
- drug-related TEAEs leading to interruption of enfortumab vedotin,
- drug-related TEAEs leading to interruption of pembrolizumab,
- grade 3 or higher TEAEs,
- grade 3 or higher drug-related TEAEs,
- TEAEs leading to death,
- drug-related TEAEs leading to death,
- TEAEs leading to death excluding disease progression,
- drug-related TEAEs leading to death excluding disease progression,
- Common TEAE that equal to or exceed a threshold of 5% in any cohort (excluding serious AEs)

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized for each cohort and overall for the following:

- TEAEs,
- drug related TEAEs,
- serious TEAEs,
- drug related serious TEAEs,
- grade 3 or higher TEAEs,
- grade 3 or higher drug-related TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- TEAEs leading to permanent discontinuation of enfortumab vedotin,
- TEAEs leading to permanent discontinuation of pembrolizumab,
- drug related TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of enfortumab vedotin,
- drug related TEAEs leading to permanent discontinuation of pembrolizumab,
- TEAEs leading to dose reduction,
- drug-related TEAEs leading to dose reduction,
- TEAEs leading to dose interruption,
- TEAEs leading to interruption of enfortumab vedotin,
- TEAEs leading to interruption of pembrolizumab,
- drug-related TEAEs leading to dose interruption,
- drug-related TEAEs leading to interruption of enfortumab vedotin,
- drug-related TEAEs leading to interruption of pembrolizumab,
- TEAEs leading to death,
- drug-related TEAEs leading to death

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

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by NCI-CTCAE grade and by relationship to study drug. If a subject has multiple TEAEs with the same SOC or PT, but with differing CTCAE grade or relationship, then the subject will be counted once with the worst nonmissing CTCAE grade and the highest degree of relationship. If CTCAE grade is missing for all episodes of the event, the subject will be counted under missing CTCAE grade. If relationship is missing for an adverse event, it’s considered to have the highest degree of relationship.

The number and percentage of subjects with treatment-emergent AESIs, as classified by AESI category and PT, will be summarized for each cohort and overall for the following:

- Treatment-emergent AESIs,
- Drug-related treatment-emergent AESIs,
- Treatment-emergent AESIs by NCI-CTCAE grade,
- Drug-related treatment-emergent AESIs by NCI-CTCAE grade,

- Serious treatment-emergent AESIs,
- Treatment-emergent AESIs leading to permanent discontinuation of study drug,
- Treatment-emergent AESIs leading to permanent discontinuation of enfortumab vedotin,
- Treatment-emergent AESIs leading to permanent discontinuation of pembrolizumab,
- Treatment-emergent AESIs leading to dose reduction,
- Treatment-emergent AESIs leading to dose interruption,
- Treatment-emergent AESIs leading to interruption of enfortumab vedotin,
- Treatment-emergent AESIs leading to interruption of pembrolizumab

For selected AESI, time to first onset of AESI, time to first onset of specific grade of AESI (e.g., grade 3 or higher, grade 2 or higher) and time to resolution will be summarized by descriptive statistics by AESI category for each cohort and overall. Time to onset will be summarized at the subject level. Time to resolution will be summarized at the event level.

For other AEs of risk for EV, it will be summarized in the same way as AESI.

For AEOSI, the following tables will be generated:

- Adverse event summary for AEOSI
- Adverse event summary by AEOSI category
- Participants with adverse events of special interest by AEOSI category and preferred term
- Participants with adverse events of special interest by AEOSI category, preferred term , and maximum toxicity grade
- Time to onset of AEOSI
- Summary of concomitant corticosteroid use for AEOSI
- Participants with AEOSI by outcome

All AEs, SAEs, deaths, withdrawals due to adverse events, AESI, other AEs of risk for EV and AEOSI will be displayed in listings.

6.5.2 Clinical Laboratory Evaluation

The baseline value will be the last nonmissing value taken on or prior to first dose of study drug.

Quantitative values evaluated by local laboratories including hematology, biochemistry, and urinalysis will be summarized using mean, standard deviation, minimum, maximum and median by cohort and overall at each analysis visit. Additionally, a within-subject change will be calculated as the postbaseline measurement minus the baseline measurement and summarized in the same way. Plots of median, 25^{th} percentile, and 75^{th} percentile lab values at each scheduled assessment time will be provided for each laboratory parameter by cohort and overall.

Laboratory results will be graded using NCI-CTCAE, where possible. Parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same subject can be counted for both values if the subject has different

laboratory values meeting each criterion. NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of subjects for each visit. Shift tables of NCI-CTCAE grade change from baseline to worst postbaseline grade for selected laboratory parameters will also be presented. The number and percentage of subjects with treatment-emergent NCI-CTCAE grade 3 or 4 laboratory results will be summarized by cohort and overall. Treatment-emergent NCI-CTCAE grade 3 or 4 laboratory results are defined as: subject's worst postbaseline NCI-CTCAE grade for a laboratory parameter being grade 3 or 4, and the worst postbaseline grade is higher than subject's baseline grade for that laboratory parameter. If baseline grade is missing, any postbaseline grade 3 or 4 laboratory result is considered as treatment-emergent. When determining the worst postbaseline value for a subject, both scheduled and unscheduled lab results collected within 30 days after the last dose of study drug will be included.

Laboratory data will be displayed in listings.

6.5.2.1 Liver Safety Assessment

The liver safety assessments will be summarized by the categories below based on the measurements from Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination. These parameters will be based on measurements from local laboratories. The normal ranges from the corresponding laboratories should be used.

The subject's highest value postbaseline (including unscheduled visits) will be used.

- ALT > 3×ULN, > 5×ULN, > 10×ULN, > 20×ULN
- AST > 3×ULN, > 5×ULN, > 10×ULN, > 20×ULN
- ALT or AST > 3×ULN, > 5×ULN, > 10×ULN, > 20×ULN
- ALP > 1.5×ULN
- Total Bilirubin > 2×ULN
- (ALT or AST > 3×ULN) and Total Bilirubin > 2×ULN *
- (ALT or AST > 3×ULN) and ALP < 2×ULN and Total Bilirubin > 2×ULN *

* Combination of values measured within the same day or up to 1 day apart

The denominator for each criterion will be the number of subjects who have at least one value postbaseline. The number and percentage of subjects meeting the criteria will be summarized by cohort and overall.

6.5.3 Vital Signs and Weight

The baseline value will be the last nonmissing value taken on or prior to first dose of study drug.

Vital signs (systolic blood pressure, diastolic blood pressure, pulse rate and body temperature) and weight will be summarized using mean, standard deviation, minimum, maximum and median by cohort (and overall) and visit. Additionally, a within-subject change will be calculated per visit as the postbaseline measurement minus the baseline measurement and summarized by cohort (and overall) and visit.

6.5.4 Electrocardiograms

ECG variables will be summarized using mean, standard deviation, minimum, maximum and median for each cohort and overall at each visit and time point, including changes from baseline. For subjects with replicate readings, mean value of replicate readings at each time point will be used in summaries.

Number and percent of subjects with normal, and abnormal results as assessed locally by investigator for overall interpretation will be tabulated by cohort and overall at each treatment visit and time point.

6.5.5 Pregnancies

A detailed listing of all pregnancies will be provided.

6.5.6 Eastern Cooperative Oncology Group Performance Status

Number of percentage of subjects for each category of the ECOG performance status at each assessment time will be provided by cohort and overall. ECOG performance status range from 0 (fully active) to 5 (dead). Negative change scores indicate an improvement and positive scores indicate a decline in performance. ECOG will also be summarized using shift table from baseline to maximum postbaseline score for each cohort and overall.

6.5.7 Ophthalmologic Assessment

The following ophthalmologic variables will be summarized by descriptive statistics and will be presented at each visit where ophthalmologic assessment is performed, by eye, cohort and overall:

- Visual acuity: method of assessment, visual acuity score (VAS)
- Slit lamp biomicroscopy: location of biomicroscopy, biomicroscopy interpretation (normal vs. abnormal)
- Tonometry: intraocular pressure result
- Dilated fundus examination: interpretation (normal vs. abnormal)

6.6 Analysis of Pharmacokinetics

Pharmacokinetic analysis will be conducted on the PKAS by cohort and overall.

Plasma concentrations of MMAE and serum concentrations of enfortumab vedotin will be summarized separately by scheduled time for each cohort and overall using descriptive statistics, including n, mean, standard deviation, coefficient of variation (CV), geometric mean, geometric CV, minimum, median and maximum. If appropriate, standard graphs of individual and mean trough concentration over time will be produced for each analyte by cohort and overall.

A separate population Pharmacokinetic Analysis Plan may be produced to describe potential model-based analyses. The results and the model development will be described in detail in a separate population pharmacokinetic report.

6.7 Interim Analysis (and Early Discontinuation of the Clinical 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 RECIST Version 1.1 by 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(one-sided) (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 (one-sided) 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 is included in Table 3. 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 3 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 3/5/6ǂ/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

ǂ Interim analysis for Cohort 6 will be conducted when applicable under protocol versions 1.0 and 2.0 based on enrollment status.

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 of overall antitumor activity (including central imaging data if available) and safety data, the sponsor will conclude that the treatment is promising if the number of minimum responders among 40 are met per Table 3; otherwise the sponsor will conclude that the treatment is not promising.

For each cohort, the interim analysis will be conducted when there are 20 subjects in RES per investigator assessment as defined in Section 4.2 are achieved. The interim analysis will include but is not limited to the following data:

- Demographics and baseline characteristics
- Disposition
- Medical and disease history
- Response related analysis including ORR, DCR, DOR, BOR and SOD per investigator assessment. Analysis based on BOR with confirmation and without confirmation will be provided.
- Available biomarker data
- Study drug exposure
- Adverse events, including SAE and AESI
- Laboratory data

The sponsor will review the interim data and make a decision on stopping/continuing the cohort enrollment. It is not the objective of the interim analyses to terminate the study early because of evidence of efficacy. Barring any unforeseen safety issues, the study is expected to continue until its scheduled completion. The details about sponsor review team membership, roles and responsivities, data cleaning and data processing requirement will be described in a separate document.

6.8 Timing of Analyses

Interim analysis for each cohort will be conducted as specified in Section 6.7.

Primary analysis will be conducted for each cohort when all subjects in a cohort have had the opportunity to be followed for at least 6 months after the first dose of study drug. At the time of primary analysis for a cohort other than the last enrolling cohort, all data for that cohort up to data cutoff will be included. For the last enrolling cohort, the following data will be included:

- Efficacy data for the last enrolling cohort up to data cutoff date.
- Non-efficacy data for all subjects from all cohorts up to data cutoff date.

The final analysis of the study will be conducted when all subjects have discontinued from the study.

A Safety Monitoring Committee (SMC) will periodically monitor the study for safety and review study safety data for all cohorts. The details will be provided in the SMC charter.

6.9 Additional Conventions

6.9.1 Analysis Windows

CRF visits will be used for analysis. For safety analysis, in the case of multiple observations at a specific visit, the observation which is closest to the target date will be used. If the observations have the same distance to the target date, the latest one will be used. If more than one observation is made on the same day, an average value if continuous or the worst value if categorical will be included in the analysis.

6.9.2 Imputation Rules for Incomplete Dates

Every effort will be made to resolve incomplete death dates. If a partial date cannot be resolved, and subject's death status is Yes, the following imputation methods will be used to complete the missing information:

- If year and/or month is missing, death date will not be imputed. Subject will be censored at the last known alive date.
- If year and month are present but date is missing, death date will be imputed as the midpoint of the earliest and the latest feasible date when last known alive date and analysis cutoff date are taken into consideration, as the examples shown in the table below.

Incomplete Date of Death (YYYY MMM DD)	Last Known Alive Date (YYYY MMM DD)	Analysis Cutoff Date (YYYY MMM DD)	Imputed Date of Death (YYYY MMM DD)
2018 APR ??	2018 MAR 15	2018 MAY 01	2018 APR 15
2018 APR ??	2018 MAR 15	2018 APR 15	2018 APR 08
2018 APR ??	2018 APR 10	2018 MAY 01	2018 APR 20
2018 APR ??	2018 APR 10	2018 APR 20	2018 APR 15

In case of partial starting date of new anti-cancer therapy and new radiation therapy, the date will be imputed to the first day of the month but no earlier than the last dosing date of the study drug. A month and year must be present or the date will remain missing.

Partial or missing date of prior therapy: for start date, the date will be imputed to the first day of the month; for the end date, the date will be imputed to the last day of the month but no later than 14 days before the first dose of the study drug. A month and year must be present or the date will remain missing.

Missing or partial start and stop dates of AEs and concomitant medication will be imputed using the following algorithm:

- Imputation rules for partial or missing stop dates:

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

- Imputation rules for partial or missing start dates:

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

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

The imputed dates will be used to determine whether an AE is/is not treatment emergent. Listings of AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

Subjects who do not satisfy the criteria to be counted as responders or have insufficient data to determine or confirm a response per the RECIST guidelines (Version 1.1) will be considered as non-responders in the final analysis of response rates. No imputation of data will be done to determine individual subject response.

For continuous variables (e.g., clinical laboratory measurement, vital signs), subjects with missing baseline variable will be excluded from the analysis of change from baseline.

For all analyses other than pharmacokinetic analysis, all values will be included in the analyses. For analysis of pharmacokinetic data, only samples for which the time of sampling relative to the dose administration and the exact dose is known will be included.

6.9.3 Outliers

All values will be included in the analyses.

7 REVISION AND RATIONALE

Version	Date	Changes	Comment/rationale for change
1.0	05-Feb-2020	NA	Document finalized
2.0	11-Feb-2022	Section 2.2 Study design was updated that subjects enrolled into Cohort 6 are reallocated to Cohort 7 and Cohort 8 based on tumor histology	Per protocol amendment 2, the mixed histology gastroesophageal cancer cohort (Cohort 6) will be split into Cohort 7 and Cohort 8 based on tumor histology to help refine efficacy signal and understand the strength of signal in each histology type.
		Section 2.2 and 5.3.2 Central images will be read after minimum number of responders at stage 1 are met based on BOP2 design	Per updates in protocol amendment 2
		Section 5.2 Update definition for DOR and PFS to censor subject who has PD or death immediately after >=2 missed tumor assessment	Update definition for DOR and PFS per FDA feedback
		Section 5.4 Update SAE definition to include important medical event process Change AESI of ocular disorders to dry eye, and corneal disorders and blurred vision	• Due to transition of always serious term process to important medical event process • To reflect the latest search criteria for AESI
		Section 5.3.5 and 6.4.3.4 Update postbaseline ATA definition Clarify that postbaseline ATA will be summarized by baseline ATA status	• Add granularity to positive ATA definition • Add clarification of ATA summary
		Section 6.2.4 Add additional types of prior systemic therapy Update summary for relapse status based on different cohort	• To provide details on prior systemic therapy of interest • Align with eligibility criteria in protocol amendment 2
		Section 6.4 Remove efficacy analysis for “overall” Remove sensitivity analysis for DCR for subjects who have been followed up for at least 6 months Remove exploratory analysis for biomarker	• Efficacy analysis is more meaningful for each distinct cancer type • Primary analysis for each cohort will ensure all subjects in the cohort have been followed for at least 6

Version	Date	Changes	Comment/rationale for change
		Add additional subgroup analysis based on prior use of anti-cancer therapy and best response to selected prior anti-cancer therapy	months, thus the sensitivity analysis will not provide additional information • Exploratory analysis for biomarker including Nectin-4 will be described in a separate biomarker SAP • Add additional subgroup analysis for prior anti-cancer therapy to cover different standard of care treatment for different cancer types.
		Section 6.5 Add overview of AE table to report number of events and events adjusted by patient year Add summaries for overview and by SOC and PT for TEAE and drug-related TEAE leading to death excluding disease progression Add summaries for SAE, >=Grade 3 TEAE, TEAE leading to discontinuation, TEAE leading to dose reduction, TEAE leading to dose interruption by descending frequency of PT Add summaries for serious AESI, AESI leading to discontinuation of study drug, AESI leading to dose reduction, AESI leading to dose interruption. Clarify analysis for laboratory evaluation and definition of treatment-emergent grade 3 or 4 laboratory results Clarify ECG interpretation category	• Add AE analysis by patient year to adjust for potential difference in drug exposure across different cohorts • Add these analyses to exclude death due to disease progression • Add these analyses to help identify the most common PTs in each category • Add additional summaries for AESIs to better characterize identified or potential risk of study drug • Apply same window as TEAE to treatment-emergent laboratory toxicity • To be consistent with information collected on eCRF
		Section 6.6 Update Table 2 to include Cohort 7 and Cohort 8	Per updates in protocol amendment 2
		Section 6.8 Update timing of primary analysis for each cohort	Due to enrollment separation of different cohort, primary analysis will be conducted for each cohort
3.0	4-Oct-2023	Section 2.1	Based on clinical data from cohort 5 in the current study, the

Version	Date	Changes	Comment/rationale for change
		Add primary objectives, secondary objectives and exploratory objectives for cohort 9 Section 2.2 Add study design for cohort 9 Section 3 Add sample size calculation for cohort 9 Sections 5.3.3 and 6.4.3.3 Add efficacy endpoints per iRECIST for cohort 9 Sections 5.3.4 and 6.4.3.4 Add cohort 9 for biomarker analysis Sections 5.3.7.2, 6.4.3.8, 6.4.3.9 and 6.4.3.10 Add PRO endpoints and analyses for cohort 9 Sections 5.4 and 6.5.1 Add TEAE definition for SAE in Cohort 9; Update drug-related TEAE definition for cohort 9; Add pneumonitis/interstitial lung disease as Other AEs of risk for EV for cohorts 1-9; Add AEOSI for cohort 9; Add TEAE analyses for cohort 9; Remove "return to baseline" for resolution; Remove improvement of AESI analysis Sections 5.5.2 and 6.3.2 Add exposure analysis for cohort 9 Section 6.2.2 Update PD3 for cohort 9 Section 6.2.3 Add cohort 9 for certain baseline characteristics Section 6.4.4 Add subgroup variables for cohort 9	data from the combination of EV and pembrolizumab in 1L urothelial cancer, and the pembrolizumab studies in HNSCC, the combination of enfortumab vedotin and pembrolizumab may have potential as a first-line treatment in PD-L1 positive subjects with recurrent/metaststic HNSCC. By following FDA's approach, definition of resolution was revised; time to improvement analysis was removed.

Version	**Date**	**Changes**	**Comment/rationale for change**
		Section 6.7 Add efficacy boundaries for cohort 9 Section 9.4 Add scoring algorithm for EORTC QLQ-HN43	
4.0	19-Mar-2025	List of abbreviation Change the description of MSD Section 5.3.3.1 Change the criteria of iSD to 7 weeks Section 5.3.3.4 Remove the derivation of missing 2 consecutive visits	Per Merck's review comments iSD should have the same criteria as SD per RECIST. Detailed derivations are saved in ADaM specifications.

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9 APPENDICES

9.1 Appendix 1: Key Contributors

List of Key Contributors and Approvers

Key Contributors

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

Primary author (s)

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9.2 Appendix 2: Author and Approver Signatures

(E-signatures are attached at the end of document.)

PPD, APGD was the study statistician for this study.

PPD, APGD was the biostatistics peer reviewer of this Statistical Analysis Plan

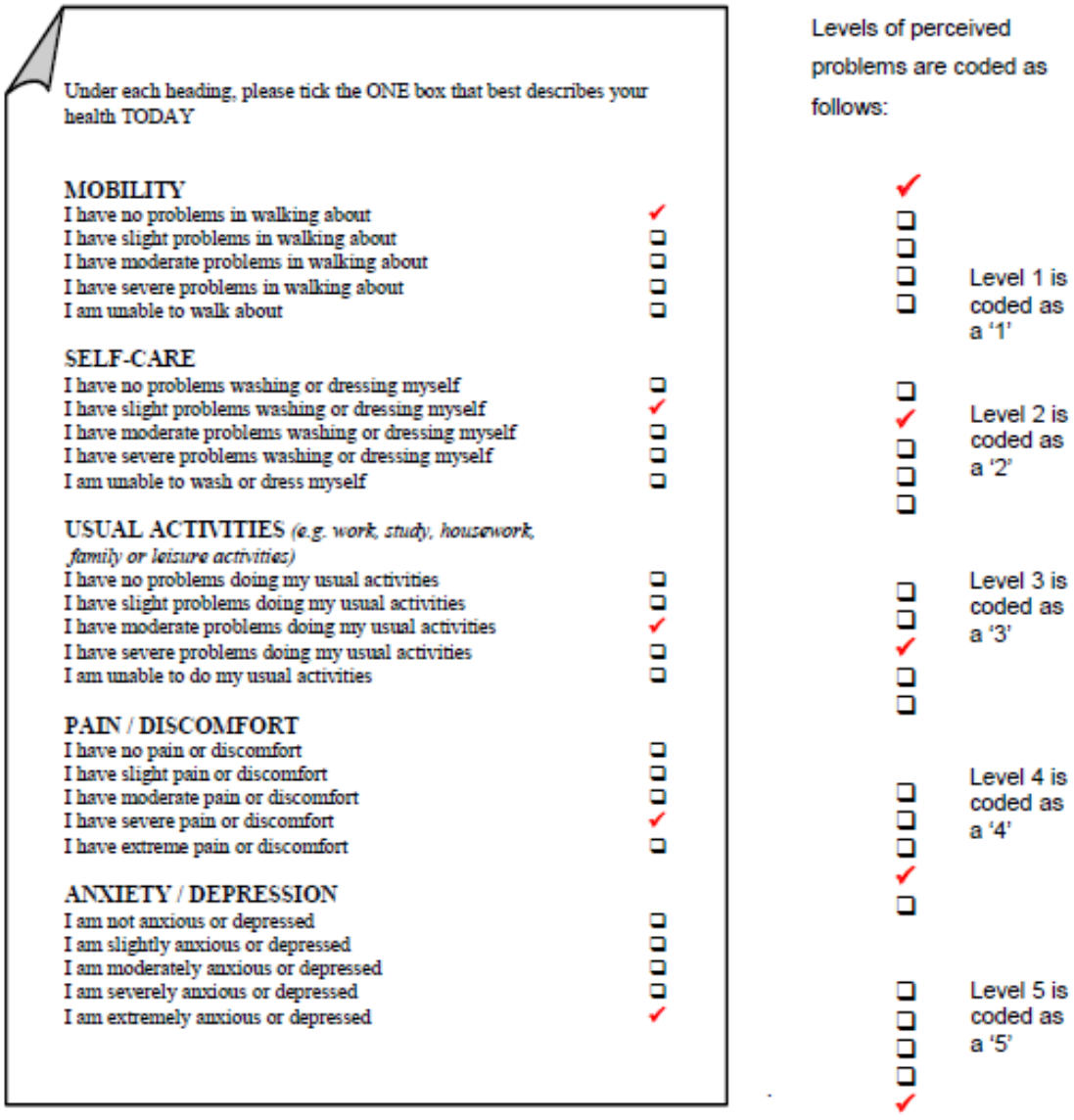
This Statistical Analysis Plan was approved by:

PPD

PPD

9.3 Appendix 3: EQ-5D-5L Scoring Algorithm

The EQ-5D-5L descriptive system should be scored, for example, as follows:



This example identifies the health state '12345'.

***NB:** There should be only ONE response for each dimension*

Using the England value set

SAS code to calculate the utility index using the England value set is presented below:

```
data mydata;
set mydata;

c0=1;
p0=(0.397*0.427+0.270*0.939+0.333*1.635);

item1=.;
if (mobility=1) then item1=0;
if (mobility=2) then item1=0.051;
if (mobility=3) then item1=0.063;
if (mobility=4) then item1=0.212;
if (mobility=5) then item1=0.275;

item2=.;
if (self_care=1) then item2=0;
if (self_care=2) then item2=0.057;
if (self_care=3) then item2=0.076;
if (self_care=4) then item2=0.181;
if (self_care=5) then item2=0.217;

item3=.;
if (usual_activity=1) then item3=0;
if (usual_activity=2) then item3=0.051;
if (usual_activity=3) then item3=0.067;
if (usual_activity=4) then item3=0.174;
if (usual_activity=5) then item3=0.190;

item4=.;
if (pain_discomfort=1) then item4=0;
if (pain_discomfort=2) then item4=0.060;
if (pain_discomfort=3) then item4=0.075;
if (pain_discomfort=4) then item4=0.276;
if (pain_discomfort=5) then item4=0.341;

item5=.;
if (anxiety_depression=1) then item5=0;
if (anxiety_depression=2) then item5=0.079;
if (anxiety_depression=3) then item5=0.104;
if (anxiety_depression=4) then item5=0.296;
if (anxiety_depression=5) then item5=0.301;

index_5L=c0-(p0*(item1+item2+item3+item4+item5));
format index_5L 5.3;

run;
```

It is to be noted that the above algorithm may lead to negative values, representing states worse than death.

9.4 Appendix 4: EORTC QLQ-HN43 Scoring Algorithm

The scoring algorithm for each symptom subscale is presented in the table below.

	Number of items (n)	Item range*	QLQ-HN43 item numbers (I_1, I_2, …, I_n)
Multi-item scales			
Pain in the mouth	4	3	31 - 34
Swallowing	4	3	35 - 38
Problems with teeth	3	3	39, 40, 73
Dry mouth and sticky saliva	2	3	42, 43
Problems with senses	2	3	44, 45
Speech	5	3	47, 55 - 58
Body image	3	3	48 - 50
Social eating	4	3	51 - 54
Sexuality	2	3	60, 61
Problems with shoulder	2	3	62, 63
Skin problems	3	3	65 - 67
Fear of progression	2	3	69, 70
Single items			
Problems opening mouth	1	3	41
Coughing	1	3	46
Social contact	1	3	59
Swelling in the neck	1	3	64
Weight loss	1	3	68

Table continued on next page

Problems with wound healing	1	3	71
Neurological problems	1	3	72

* "Item range" is the difference between the possible maximum and the minimum response for individual items. All items are scored 1 to 4, giving range = 3.

How to score:

1) Raw score
   For each multi-item scale, calculate the average of the corresponding items.
   Raw score = RS = $\frac{(I1+I2+\cdots+In)}{n}$

   For each single-item measure, the score of the concerning item corresponds to the raw score.

2) Linear Transformation
   To obtain the Score S, standardize the raw score to a 0-100 range using the following algorithm:
   S = $\frac{(RS-1)}{range} * 100$

Missing data

Missing data may be classified as either missing items (one or more missing answers to questions within a questionnaire), or missing forms (the whole questionnaire is missing for a patient).

- If at least half of the items from the scale have been answered, use all the items that were completed, and apply the standard equations to calculate raw scores and scores; ignore any items with missing values when making the calculations.

  For example, Question 35 of swallowing scale is missing. Raw score = (Question 36 + Question 37 + Question 38)/3. Score = $\frac{(RS-1)}{range} * 100$
- Otherwise, set scale score to missing.
- For single-item measures, set score to missing.