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SeattleGenetics

STATISTICAL ANALYSIS PLAN

Protocol Number:	SGN22E-001
Version:	Version 4 17-Sep-2020
Protocol Title:	A single-arm, open-label, multicenter study of enfortumab vedotin (ASG-22CE) for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor (CPI) therapy
Study Sponsor:	Seattle Genetics, Inc. 21823 30th Drive SE Bothell, WA 98021, USA
IND Sponsor:	Astellas Pharma Global Development, Inc. (APGD) 1 Astellas Way. Northbrook, IL 60062, USA

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APPROVAL SIGNATURES

Product:	Enfortumab vedotin (ASG-22CE)
Protocol Number/Amendment:	SGN22E-001 / Amendment 6
SAP Version:	Version 4
Version Date:	17-Sep-2020

The individuals signing below have reviewed and approve this statistical analysis plan.

[redacted]

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LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ATA	antitherapeutic antibodies
CDISC	clinical data interchange standards consortium
CI	confidence interval
CPI	checkpoint inhibitor
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EOS	end of study
EOT	end of treatment
EQ-5D	EuroQol five dimensions
IDMC	independent data monitoring committee
IRF	independent review facility
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Affairs
MMAE	monomethyl auristatin E
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PP	per protocol
PR	partial response
PRO	patient reported outcome
PT	preferred term
QLQ-C30	EORTC Quality of Life Questionnaire
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
SAE	serious adverse event
SMQ	standard MedDRA query
TEAE	treatment emergent adverse event
SD	stable disease
SOC	system organ class
SSQ	sponsor specified query
VAS	visual analog scale
WHO	World Health Organization

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1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGN22E-001, entitled "A single-arm, open-label, multicenter study of enfortumab vedotin (ASG-22CE) for treatment of patients with locally advanced or metastatic urothelial cancer who previously received immune checkpoint inhibitor (CPI) therapy". Results of the proposed analyses will become the basis of the clinical study report (CSR) for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the final CSR. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the CSR.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To determine the antitumor activity of single-agent enfortumab vedotin as measured by confirmed objective response rate (ORR) in patients with locally advanced or metastatic urothelial cancer who have previously received systemic therapy with a CPI and either received platinum-containing chemotherapy or are platinum-naïve and cisplatin-ineligible

2.2 Secondary Objectives

- To assess duration of response (DOR)
- To assess disease control rate (DCR)
- To assess progression-free survival (PFS)
- To assess overall survival (OS)
- To assess the safety and tolerability of enfortumab vedotin
- To assess the pharmacokinetics (PK) of enfortumab vedotin
- To assess the incidence of antitherapeutic antibodies (ATA)

2.3 Additional Objectives

- To explore potential correlations between biomarkers and clinical outcomes
- To evaluate the treatment effect of enfortumab vedotin on quality of life (QoL)

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3 STUDY ENDPOINTS

3.1 Primary Endpoint

The primary efficacy endpoint of this study is ORR (confirmed complete response [CR] or partial response [PR] per Response Evaluation Criteria in Solid Tumors [RECIST] Version 1.1) as determined by an independent review facility (IRF)

3.2 Secondary Endpoints

- DOR (confirmed CR or PR) per IRF
- DCR_{16} (DCR [CR, PR or stable disease (SD)] at 16 weeks) per IRF
- PFS per IRF
- ORR per investigator assessment
- DOR per investigator assessment
- DCR_{16} per investigator assessment
- PFS per investigator assessment
- OS
- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs)
- Laboratory abnormalities
- Selected plasma or serum PK parameters of enfortumab vedotin and monomethyl auristatin E (MMAE)
- Incidence of ATA to enfortumab vedotin

3.3 Additional Endpoints

- Biomarkers of biological and clinical activity, including Nectin-4 expression
- Patient reported outcomes (PRO) per the EORTC Quality of Life Questionnaire (QLQ-C30)
- PRO per EuroQol 5-dimensions (EQ-5D), including health utility values, and visual analog scale

4 STUDY DESIGN

This is a single-arm, open-label, multicenter trial designed to assess the efficacy and safety of enfortumab vedotin as a single agent in locally advanced or metastatic urothelial cancer subjects who have previously received systemic therapy with a CPI. Subjects must also either have received prior treatment with platinum-containing chemotherapy (Cohort 1) or received no prior platinum-containing or other chemotherapy and are ineligible for treatment with

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cisplatin (Cohort 2). Subjects must have progressive disease (PD) during or following their most recent therapy. There are no limits for prior lines of therapy, including taxanes.

Enfortumab vedotin at a dose of 1.25 mg/kg will be administered as an intravenous infusion on Days 1, 8, and 15 of each 28-day cycle. Subjects will continue to receive study treatment until disease progression, unacceptable toxicity, investigator decision, consent withdrawal, start of subsequent anticancer therapy, pregnancy, or study termination by the sponsor. Subjects who discontinue study treatment for reasons other than disease progression per RECIST v1.1 or start of subsequent anticancer therapy will continue to have response assessments, Eastern Cooperative Oncology Group (ECOG) performance status, and physical exams every 8 weeks (±1 week). After 1 year on study, the frequency of follow-up exams including response assessments will be reduced to every 12 weeks (±1 week). Subjects who have progressed or begun subsequent anticancer therapy will be contacted every 8 weeks (±1 week) up to 1 year on study, and every 12 weeks (±1 week) thereafter to obtain information on subsequent anticancer therapy, and survival status until death, study closure, withdrawal of consent, or subject is lost to follow-up, whichever occurs first (see Figure 1). The study will be closed 5 years after enrollment of the last subject, or when no subjects remain in long-term follow-up, whichever occurs first. Additionally, the sponsor may terminate the study at any time.

Measures of anticancer activity will be assessed by radiographic tumor imaging at protocol-specified timepoints. Tumor response will be assessed locally and centrally by an IRF according to RECIST v1.1 (Eisenhauer 2009). Clinical response of CR, PR, SD, or PD will be determined at each assessment. Responses (CR or PR) will be confirmed with repeat scans at least 4 weeks after first documentation of response. Tumor assessments will continue until the subject has radiologically-confirmed disease progression per RECIST v1.1 by the investigator, initiates a new anticancer therapy, dies, withdraws consent, or the study closes, whichever comes first.

Safety assessments will be based on the information collected through the safety surveillance process and will include the data from recorded AEs including serious adverse events (SAEs), recording of concomitant medication, medical history, physical examination findings, and laboratory tests.

Approximately 200 subjects will be enrolled in this study, including approximately 100 or more platinum-treated subjects (Cohort 1) and up to approximately 100 platinum-naïve and cisplatin-ineligible subjects (Cohort 2).

On a periodic basis, approximately every 3 months until all treated subjects in Cohort 1 have had the opportunity to be followed for at least 6 months and at a frequency considered adequate based on the rate of enrollment to Cohort 2 thereafter, an independent data monitoring committee (IDMC) will monitor the safety of subjects participating in this trial. The IDMC will be guided by an independent charter and will be responsible for evaluating the results of safety analyses and will make recommendations to the sponsor. The IDMC may also request efficacy data, if needed, to evaluate risk/benefit before making

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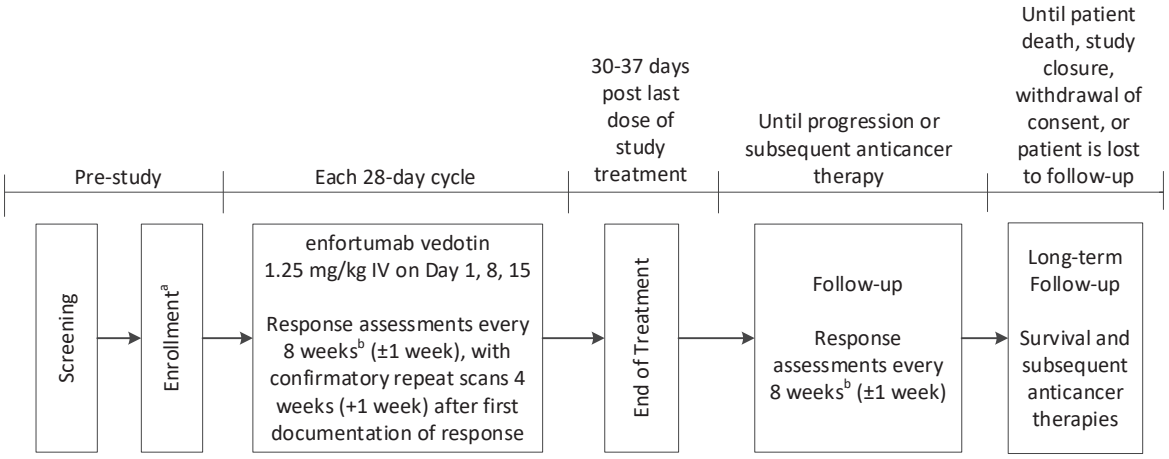
recommendations. The IDMC will make recommendations to either continue the study unchanged, modify the study, or discontinue the study. The final decision to act on the IDMC recommendations will be made by the sponsor.

An ongoing real-time review of subject safety and SAEs will also be conducted by the sponsor's Drug Safety Department.

Figure 1 Study Schema



a There are 2 cohorts of CPI-treated patients in the study: Cohort 1) platinum-treated patients, and Cohort 2) platinum-naïve/cisplatin-ineligible patients.
b After 1 year on study, the frequency of response assessments will be reduced to every 12 weeks (±1 week).

A detailed study assessment schedule can be found in the protocol.

5 ANALYSIS SETS

5.1 Full Analysis Set

The full analysis set will include all subjects who are enrolled in the study and receive any amount of enfortumab vedotin.

The full analysis set will be used as the primary analysis set for efficacy endpoints. Subject demographics and baseline disease characteristics will be summarized based on the full analysis set.

5.2 Safety Analysis Set

The safety analysis set will include all subjects who receive any amount of enfortumab vedotin, and thus is equivalent to the full analysis set defined in this protocol. The safety analysis set will be used for all safety analyses.

5.3 Efficacy Evaluable Set

The efficacy evaluable set will include all subjects in the full analysis set who started treatment with enfortumab vedotin at least 8 months before the analysis data cutoff. The efficacy evaluable set will be used for the additional analyses of efficacy endpoints at the

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time of the Cohort 2 interim analyses to allow adequate follow up for a stable estimate of ORR and DOR.

5.4 Pharmacokinetics (PK) Analysis Set

The PK analysis set will include all subjects who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, MMAE or TAb concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin, MMAE and TAb concentration data. The PK analysis set will be used for PK analyses.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

In general, all analyses will be performed separately for each cohort and the 2 cohorts combined, unless otherwise specified. Descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages (of non-missing) per category for categorical variables.

Unless otherwise specified, confidence intervals (CIs) will be calculated at two-sided 95% level.

The two-sided 95% exact CI using the Clopper-Pearson method will be calculated for the response rates where applicable (e.g., ORR) (Clopper 1934).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Any analysis not described in this plan will be considered exploratory, and will be documented in the CSR as a post hoc analysis.

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created and attached to Section 16 of the study report.

All statistical Tables, Listings and Figures will be produced using SAS®, version 9.3 or higher. Sample size calculations were performed using EAST®, version 6.0. Other statistical software, if used, will be described in the CSR.

6.2 Determination of Sample Size

The study is designed to estimate the confirmed ORR in the full analysis set and to detect an improvement in the ORR compared with a historical 10% response rate.

The primary efficacy hypothesis is

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$$H_0: ORR \leq 10\% \ \ vs. \ \ H_a: ORR > 10\%$$

Approximately 200 subjects will be enrolled to ensure collection of sufficient efficacy and safety data, including approximately 100 or more platinum-treated subjects (Cohort 1) and up to approximately 100 platinum-naïve and cisplatin-ineligible subjects (Cohort 2). Using the estimate of approximately 100 subjects in Cohort 1, the study will have 98% power to detect a 15% increase in ORR from 10% to 25%, and 81% power to detect a 10% increase in ORR from 10% to 20%, at one-sided significance level of 0.025, based on exact methods using EAST®, Version 6.0, by Cytel Inc.

The confirmed ORR and 95% exact CI for subjects in Cohort 2 will be summarized at 4 timepoints:

1) at the time of the primary analysis of Cohort 1 (i.e., after all subjects in Cohort 1 have had the opportunity to be followed for at least 6 months),
2) when approximately 50 subjects in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin,
3) when approximately 70 subjects in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, and
4) when all subjects in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin.

For illustration purpose, assuming the observed ORR in Cohort 2 is 30%, the 95% exact CIs of ORR based on the expected number of subjects at each analysis timepoint are summarized below:

Number of Subjects	95% Exact CI
N=20	(12%, 54%)
N=50	(18%, 45%)
N=70	(20%, 42%)
N=100	(21%, 40%)

Sample Size for IDMC Assessment of Slit Lamp Examination

Slit lamp examinations will be conducted on at least the first 60 enrolled subjects (from Cohorts 1 and/or 2) on Cycle 2 Day 22 (±1 week) and Cycle 6 Day 22 (±1 week). If treatment-emergent corneal events are observed in <15% of the first 60 enrolled subjects and if the events are generally low grade or asymptomatic, the IDMC may make a recommendation to cease Cycle 2 Day 22 and/or Cycle 6 Day 22 slit lamp exams for the remaining subjects if warranted based on review of the cumulative ocular safety data. Based on the results from the Phase 1 study (Study ASG-22CE-13-2), as of the data cutoff date of 14 November 2016, there were 3 subjects who reported experiencing corneal adverse events out of 33 subjects (9%) on 1.25 kg/mg of enfortumab vedotin. Assuming an event rate of 9%,

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with a sample size of 60, the probability of observing >3 events (5%) is 80.0% and the probability of observing <9 events (15%) is 91.2%. If the event rate is higher, the probability of observing <9 events is decreased. For example, if the event rate is 20%, the probability of observing <9 events is decreased to 12.7%.

6.3 Randomization and Blinding

This is a single-arm, open-label study. No randomization or blinding will be used.

6.4 Data Transformations and Derivations

6.4.1 General

Reported age in years will be used; if not available, age at informed consent in years will be calculated with the SAS® INTCK function (with method specified as "continuous") using informed consent date and birth date.

Study Day will be calculated as (Date – First Dose Date + 1) for dates on or after the first dose date. The date of first dose will be Study Day 1. For dates prior to the first dose date, Study Day will be calculated as (Date – First Dose Date). For example, the date before the first dose date will be Study Day -1.

Other time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

The following unit conversion will be implemented unless otherwise specified:

Months=Days/30.4375

Years=Days/365.25

Unless otherwise specified, baseline values used in all analyses will be the most recent non-missing measurement prior to the first dose of study drug.

6.4.2 Best Overall Response

The subject's best overall response per IRF will be the best demonstrated response to date that has been confirmed, when confirmation is required (i.e. for PR and CR). Response after the start of subsequent anticancer therapy will not be included in the derivation of best overall response. The subject's best overall response will be used in determining the ORR per IRF.

A response (CR or PR) will be considered confirmed if the subsequent response assessment (at least 4 weeks after the initial response) still shows response (CR or PR). A subject will have a best response of SD if there is at least one SD assessment (or better) ≥6 weeks after the start of treatment and the subject does not qualify for confirmed CR or PR. RECIST v1.1 outlines scenarios for best overall responses when confirmation of CR and PR is required.

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6.4.3 Response Assessment Dates

At each response assessment time point, scans to evaluate target and non-target lesions can be performed on multiple dates. If the time point response is CR or PR, then the latest date of all radiologic scans at the given response assessment visit will be the date of response. If the time point response is SD, then the earliest date of all radiologic scans at the given response assessment visit will be the date of SD. If the time point response is PD, then the earliest date that PD has been documented will be the date of PD, i.e. the earliest of:

- Date of target lesion assessments when the target lesion response is PD
- Date of non-target lesion assessments when the lesion status is unequivocal progression
- Date of documenting new lesions

For subjects whose best overall response is a confirmed CR or PR, the date of objective response will be the date of initial documentation of response (i.e., CR or PR that is subsequently confirmed).

6.4.4 Adequate Response Assessment

An adequate tumor assessment must include a radiologic scan with the overall disease response of CR, PR, SD, or PD.

6.4.5 Action Taken with Study Treatment of Adverse Events

Action taken with study treatment of each adverse event (AE) will be mapped to the Clinical Data Interchange Standards Consortium (CDISC) controlled terminology as listed below:

1. dose not changed
2. dose reduced
3. drug interrupted
4. drug withdrawn

Drug interruption includes dose elimination, dose delay, infusion interruption with full dose received, and infusion stop early without full dose received, as collected on the case report form (CRF). If more than one action is associated to an AE, the action taken that is the end result will be selected.

6.5 Handling of Dropouts and Missing Data

Missing data will not be imputed unless otherwise specified.

For time-to-event endpoints (e.g., duration of response, PFS, and OS), subjects who have no specified event will be censored as specified for each respective endpoint in Section 7.5.

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Subjects who do not have at least two (initial response and confirmation scan) post-baseline response assessments will be counted as non-responders for the analysis of primary endpoint.

Missing AE dates will be imputed for the purpose of calculating duration of events and treatment-emergent status (see Appendix A for imputation details and Appendix B for treatment-emergent definition).

Missing prior therapy dates will be imputed for the purpose of calculating the time from prior therapy to first dose of study drug (see Appendix C for details).

Missing subsequent anticancer therapy start date will be imputed for the purpose of deriving the time-to-event endpoints as applicable (see Appendix D for details).

Unless otherwise specified, if the numeric value of a laboratory test is not available because it is below the lower limit of quantification (LLOQ), the result will be analyzed as equal to the LLOQ when a numeric value is required (e.g., calculating the mean) and be listed as "< LLOQ" in the listings.

6.6 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough subjects to warrant an analysis by center.

6.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned and no alpha adjustment is needed because only one primary endpoint will be tested in this single-arm study.

6.8 Examination of Subgroups

As exploratory analyses, subgroup analyses will be conducted for selected endpoints. Subgroup analyses to be conducted are:

- Age (<65, ≥65 years old)
- Age (<75, ≥75 years old)
- Sex (female, male)
- Race (white, non-white)
- ECOG performance score at baseline (0, 1-2)
- Bellmunt risk score (0-1, ≥2) (Bellmunt 2010)
- Baseline weight (≤100, >100 kg)
- Primary tumor sites (upper tract, bladder/other)
- Liver metastasis (yes, no)
- Number of prior systemic therapy in locally advanced or metastatic setting (1-2, ≥3)

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- Best response to prior CPI (responder, non-responder)
- PD-L1 CPS (<10, ≥10)

A subgroup analysis may not be performed if the number of subjects in the subgroup is not sufficiently large (i.e., <10% of the full analysis set for a given cohort). At the time of the primary analysis of Cohort 1, subgroup analysis will be performed for Cohort 1 only, without including Cohort 2 subjects.

6.9 Covariates

No adjustment for covariates is planned in the analyses.

6.10 Timing of Analyses

The primary analysis of Cohort 1 (platinum-treated subjects) will be conducted when enrollment is completed in Cohort 1 and all subjects in this cohort have been followed for at least 6 months, discontinued from study, or had 30 days safety follow up after PD, whichever comes first.

Analysis for Cohort 2 will occur at 4 timepoints;

1) at the time of the primary analysis of Cohort 1,
2) when approximately 50 subjects in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin,
3) when approximately 70 subjects in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin, and
4) when all subjects in Cohort 2 have had the opportunity to be followed for approximately 8 months from the first dose of enfortumab vedotin.

Additional cutoff dates may be defined and corresponding database locks may occur to allow for more precise estimates of time-to-event endpoints.

7 PLANNED ANALYSES

7.1 Disposition

Subject disposition will be summarized for all enrolled subjects with descriptive statistics. Subjects who discontinue study treatment and subjects who withdraw from the study will be summarized along with the reason for discontinuation or withdrawal.

The number of subjects who signed informed consent, number of screen failures, and the reason for screen fail will be summarized for all screened subjects. The number of subjects enrolled at each site will be summarized.

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7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age at consent, sex, ethnicity, race, baseline height, weight, body mass index, ECOG performance status, estimated creatinine clearance, hemoglobin A1c, smoking status, and Bellmunt risk factors will be listed and summarized with descriptive statistics for the full analysis set.

Disease specific characteristics, including time from diagnosis of locally advanced/metastatic disease to enrollment, histology, current extent of disease, disease stage, primary tumor location, and metastases sites will be listed and summarized for the full analysis set.

Summary of prior cancer-related therapies, including number of prior therapies, therapy type, setting of prior therapies, best response to prior therapies, time from most recent prior therapy to first dose of study drug, and prior cystectomy and nephrectomy, will be presented for the full analysis set.

In addition, the pre-existing conditions that are ongoing at baseline will be summarized.

7.3 Protocol Deviations

Important protocol deviations are a subset of protocol deviations that may represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the subject's rights, safety, or welfare. Important protocol deviations also include exemptions to the study inclusion/exclusion criteria and will be summarized by category. A list of subjects with important protocol deviations will be presented.

7.4 Treatment Administration

Treatment administration will be summarized for the safety analysis set. Summary statistics for duration of treatment (weeks), number of cycles, and the number and percentage of subjects who were treated at each cycle will be presented. In addition, number of infusions per subject, cumulative dose administered, absolute dose intensity (ADI), and relative dose intensity (RDI) will be described. The number and percentage of subjects whose dose was ever modified will be summarized.

Duration of treatment is defined as time from the first study dose to the earliest of the following:

- Day 28 of the last treatment cycle
- Date of death
- Analysis cutoff date if the subject is still on treatment at the time of the analysis
- Start of subsequent anticancer therapy

Intended dose intensity (IDI) is defined as the intended dose of study drug per unit of time according to the protocol (i.e., 3.75 mg/kg/4-wk cycle).

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ADI is defined as the actual dose of study drug per unit of time that a subject received over the entire treatment period. For the purpose of calculating ADI, treatment period is defined as time from the first dose of study drug to Day 28 of the last treatment cycle, regardless if death occurs before the end of the cycle.

RDI is defined as the ADI over the IDI (i.e., RDI = ADI/IDI * 100%).

7.5 Efficacy Analyses

The primary analysis of efficacy endpoints will be performed using the full analysis set. Sensitivity analysis of the primary efficacy endpoint will be presented using the efficacy evaluable set.

7.5.1 Primary Efficacy Endpoint - Objective Response Rate (ORR) per IRF

The primary endpoint of this study is the confirmed ORR per IRF. ORR is defined as the proportion of subjects whose best overall response is a confirmed CR or PR according to RECIST v1.1 (Eisenhauer 2009). Subjects who do not have at least two (initial response and confirmation scan) post-baseline response assessment will be considered non-responders.

The primary efficacy hypothesis is outlined in Section 6.2.

The ORR per IRF and its exact two-sided 95% CI will be calculated for the full analysis set.

In addition, the ORR per IRF will be summarized and presented graphically by the subgroups defined in Section 6.8.

The maximum percent reduction from baseline in the sum of diameters per IRF will be calculated for each subject and presented graphically with a waterfall plot.

Time to response per IRF will be calculated as the time from the first dose of study drug to the first documentation of objective response (CR or PR that is subsequently confirmed). Time to response per IRF will be summarized for the responders only. Subgroup analysis of time to response will be performed for subjects who responded to the prior CPI therapy versus those who did not respond to the prior CPI therapy.

7.5.2 Objective Response Rate (ORR) per investigator

The ORR per investigator and its two-sided 95% exact CI will be calculated for the full analysis set.

The ORR per investigator in the subgroups will be presented graphically. The maximum percent reduction from baseline in sum of diameters per investigator will be calculated for each subject and presented graphically with a waterfall plot.

Time to response per investigator will be analyzed in the same way as the time to response per IRF.

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7.5.2.1 Concordance between Investigator and IRF Assessment

A summary of the concordance between investigator and IRF assessment will be provided. The percent agreement will be calculated as the proportion of subjects whose best overall response per IRF match the best overall response per investigator.

Percent agreement = (Number of matched responders + Number of matched non-responders) / Total number of subjects assessed.

7.5.3 Duration of Response

DOR is defined as the time from the date of first documented response (CR or PR that is subsequently confirmed) to the date of first documented PD per RECIST v1.1 or death due to any cause, whichever comes first.

DOR will be censored as described below:

- Subjects who do not have PD and are still on study at the time of an analysis will be censored at the date of the last adequate response assessment documenting absence of PD
- Subjects who have started a new anticancer treatment (with the exception of palliative radiotherapy on a non-target lesion that is not progressing) prior to documentation of PD will be censored at the date of the last adequate response assessment prior to start of new treatment
- Subjects who discontinue from the study prior to documentation of PD will be censored at the date of the last adequate response assessment documenting absence of PD.

DOR per IRF will only be calculated for subjects achieving a confirmed CR or PR per IRF. DOR will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median DOR and its two-sided 95% CI will be calculated. In addition, the DOR at 6 and 12 months will be summarized.

Sensitivity Analysis

The following sensitivity analysis will be performed for the DOR per IRF:

1. A sensitivity analysis to censor subjects who progressed or died after an extended loss to follow up (i.e., ≥2 consecutive missed response assessments) at the date of the last adequate response assessment prior to the missed visits.

DOR per investigator will be analyzed in the same way as the DOR per IRF.

7.5.4 Disease Control Rate at Week 16 (DCR_{16})

DCR_{16} per IRF is defined as the proportion of subjects with CR, PR, or SD at Week 16 (±1 week) based on IRF assessment. Responses do not need to be confirmed for the purpose of determining DCR_{16}. Subjects whose disease status cannot be assessed or have a missing

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assessment at Week 16 will be considered not having disease control at Week 16. The only exception is for subjects who have a CR, PR, or SD at the visits subsequent to Week 16; these subjects will be considered to have disease control at Week 16 although the Week 16 assessment is missing or not evaluable.

DCR_{16} per IRF will be summarized for the full analysis set. The exact two-sided 95% CI will be calculated.

DCR_{16} per investigator will be analyzed in the same way as the DCR_{16} per IRF.

7.5.5 Progression-free Survival (PFS)

PFS is defined as the time from start of study treatment to first documentation of PD per RECIST v1.1 or death due to any cause, whichever comes first.

The same censoring rules as outlined in Section 7.5.3 for DOR will be applied to PFS. In addition, subjects who are not known to have died and do not have any post-baseline response assessment will be censored at the date of first dose.

PFS per IRF will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS and its two-sided 95% CI will be calculated. In addition, the 6- and 12-month PFS rates will be summarized.

Sensitivity Analysis

The following sensitivity analysis will be performed for the PFS per IRF:

1. A sensitivity analysis to censor subjects who progressed or died after an extended loss to follow up (i.e., ≥2 consecutive missed response assessments) at the date of the last adequate response assessment prior to the missed visits.

PFS per investigator will be analyzed in the same way as the PFS per IRF.

7.5.6 Overall Survival (OS)

OS is defined as the time from start of study treatment to date of death due to any cause. In the absence of death, OS will be censored at the date the subject is last known to be alive or at the analysis cutoff date, whichever is earlier. Subjects who died after the analysis cutoff date will be censored at the analysis cutoff date. Subject lacking data beyond start of study treatment will have their survival time censored on the date of first dose.

OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median OS and its two-sided 95% CI will be calculated. In addition, the 6- and 12-month OS rates will be summarized.

7.6 Safety Analyses

The safety analysis set will be used to summarize all safety endpoints.

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Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0 or higher).

Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.03 or higher).

Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (version: June 2016 or more recent).

7.6.1 Adverse Events

Adverse events (AEs) will be summarized by MedDRA preferred term (PT) in descending frequency of occurrence unless otherwise specified. For incidence reporting, if a subject reports more than one AE that was coded to the same system organ class (SOC) or PT, the subject will be counted only once for that specific SOC or PT.

A treatment-emergent adverse event (TEAE) is defined as a newly occurring or worsening AE after the first dose of study treatment. See Appendix B for details regarding treatment-emergent classification.

An overall summary of TEAEs will be provided. Summaries of TEAEs by MedDRA classification will also be provided for the following:

- TEAEs
- Grade 3 or higher TEAEs
- Serious TEAEs
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- TEAEs leading to treatment discontinuation
- TEAEs leading to death
- Treatment-related TEAEs
- Treatment-related grade 3 or higher TEAEs
- Treatment-related serious TEAEs
- Treatment-related TEAEs leading to dose interruption
- Treatment-related TEAEs leading to dose reduction
- Treatment-related TEAEs leading to treatment discontinuation
- Treatment-related TEAEs leading to death
- TEAEs by SOC, PT and maximum severity. At each SOC or PT, multiple occurrences of events within a subject are counted only once at the highest severity

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- TEAEs by SOC and PT

All TEAEs, grade 3 or higher TEAEs, serious TEAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to death will be listed.

7.6.1.1 Adverse Events of Special Interest

Peripheral neuropathy, corneal events, hyperglycemia, dermatological reactions, and infusion related reactions (IRR) are considered adverse events of special interest (AESI) for enfortumab vedotin. These are medical concepts of composite terms based on the search criteria (standard MedDRA query [SMQ] or sponsor specified query [SSQ]). Other AEs may be added to AESI as necessary. The search criteria for AESI will be maintained in a separate document and finalized prior to final database lock.

Treatment-emergent AESI will be summarized by PT and maximum severity. In addition, serious AESI, treatment-emergent AESI that are related to study drug, leading to dose modification and study treatment discontinuation will be summarized.

For selected AESI, time to onset, improvement, or resolution will be analyzed as appropriate.

Time to onset of a specific AESI will be calculated as time from the first dose of study drug to the start of first treatment-emergent event that meets the respective search criteria. In the analysis of time to onset of AE of a specific grade (e.g., grade 3 or higher), episode of events that are improved from a previous higher grade will not be included.

Resolution is defined as event outcome of ‘recovered/resolved’ or ‘recovered/resolved with sequelae’, or returning to baseline grade as of the latest assessment for conditions that are ongoing at baseline. For events with an outcome of ‘recovered/resolved’ or ‘recovered/resolved with sequelae’, time to resolution will be calculated as time from the event start date to end date. For events that return to baseline grade, time to resolution will be calculated as time from the start of treatment-emergent event to the date the event was last assessed.

For events that are not resolved, improvement is defined as decrease by at least one grade from the worst grade as of the latest assessment. For events that meet the definition of ‘improvement’, time to improvement will be calculated as time from the worst grade of the event to the date the event was last assessed.

Time to onset will be summarized at the subject level. Time to resolution and improvement will be summarized at the event level.

7.6.1.2 Eye examination and Corneal AEs

The data for eye examination (complete eye examination and slit lamp examinations) at baseline and post-baseline visits will be listed. Structural corneal abnormality will be reported by the investigators and corneal events will be identified by the corneal disorders SMQ (narrow scope).

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The number and percentage of subjects with slit lamp examination performed at the protocol specified timepoints, the number and percentage of subjects with corneal events at baseline, and the number and percentage of subjects with treatment-emergent corneal events at Cycle 2 Day 22 and Cycle 6 Day 22 will be summarized. In addition, treatment-emergent corneal events will be summarized separately for subjects with and without corneal event at baseline.

7.6.2 Clinical Laboratory Parameters

All laboratory results (hematology and serum chemistry) up to the end of treatment visit will be presented in standardized units. Both observed value and changes from baseline will be summarized with descriptive statistics for each scheduled visit. Shift from baseline to maximum post-baseline NCI CTCAE grade will be summarized for each lab test. Treatment-emergent laboratory abnormalities will also be summarized.

Laboratory results and NCI CTCAE grades for hematology and serum chemistry will be presented in data listings. Normal ranges will be documented and out-of-range values will be flagged. A separate listing of laboratory results with CTCAE grade 3 or higher will be presented.

7.6.2.1 Liver Safety Assessment

The liver safety assessment will be summarized based on the measurements of alkaline phosphatase (ALP), alanine transaminase (ALT), total bilirubin, aspartate transaminase (AST), and their combination as defined below. The number and percentage of subjects meeting the criteria post-baseline will be summarized.

- ALT: > 3xULN, > 5xULN, > 10xULN, > 20xULN
- AST: > 3xULN, > 5xULN, > 10xULN, > 20xULN
- ALT or AST: > 3xULN, > 5xULN, > 10xULN, > 20xULN
- ALP: > 1.5xULN
- Total bilirubin: > 2xULN
- (ALT or AST > 3xULN) and Total bilirubin > 2xULN*
- (ALT or AST > 3xULN) and Total bilirubin > 2xULN and ALP < 2xULN*

*Combination of values measured on the same day or within 1 day apart.

In addition, subjects with the post-baseline liver function test results that are consistent with the Hy's law criteria will be listed.

7.6.3 Electrocardiogram

ECG variables will be summarized with descriptive statistics for each scheduled visit. The number and percentage of subjects with normal and abnormal results for the overall interpretation will be tabulated.

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7.6.4 Vital Signs

Vital sign measurements, including heart rate, diastolic and systolic blood pressure, and temperature, will be listed by subject and visit.

7.6.5 Concomitant Medications

Concomitant medications will be summarized by the WHO Drug ATC class and preferred name. The number and percentage of subjects who take concomitant medications will be tabulated. Concomitant medications will be listed by subject. In addition, concomitant medications for treatment of peripheral neuropathy, corneal events, hyperglycemia, rash and IRR will be presented in separate listings.

7.7 Additional Analyses

7.7.1 Patient Reported Outcomes

7.7.1.1 EORTC QLQ-C30

For each QLQ-C30 scale, score will be calculated and missing data will be accounted for according to the EORTC QLQ-C30 scoring manual. Descriptive summary of actual value and change from baseline will be presented by visit using the full analysis set.

The number and percentage of subjects with an improvement of ≥10 points from baseline in global health status/QoL scale will be summarized by visit.

The compliance and completion rate of EORTC QLQ-C30 will be summarized for each visit. Compliance rate is defined as the proportion of subjects who completed the instrument among those who are expected to complete at a given visit. Completion rate is defined as the proportion of subjects who completed the instrument among the full analysis set.

7.7.1.2 EuroQol-5D

The EQ-5D health state dimension scores will be converted into a health state index using the time trade-off valuation method and the US-based value set (Shaw 2005). Change from baseline in EQ-5D health state index and visual analogue scale (VAS) will be summarized with descriptive statistics by visit using the full analysis set.

The compliance and completion rate of EQ-5D will be summarized for each visit.

7.7.2 Subsequent Cancer-Related Therapy

The number and percentage of subjects who receive subsequent cancer-related therapies, including palliative radiotherapy, systemic therapy for disease progression, maintenance, and systemic therapy for secondary malignancy, will be summarized for the full analysis set. In addition, time from last dose of study treatment to the first subsequent anticancer therapy and time from last dose of study treatment to the first subsequent systemic therapy for disease progression will be summarized.

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7.7.3 Pharmacokinetics

Concentrations of ADC, MMAE, and TAb will be summarized using descriptive statistics (including geometric mean and coefficient of variation) at each PK sampling time point for the PK analysis set. PK parameters will be summarized using descriptive statistics. Geometric mean estimates of selected PK parameters will be compared as a ratio of drug product manufacturing process (Process B to Process A).

Additional PK and PK/pharmacodynamic analyses may be performed and be presented in a separate report. Data from this study may be combined with data from previous studies for population PK and PK/pharmacodynamic analyses. If performed, these analyses will be described in a separate analysis plan and the results will be reported separately from the CSR.

7.7.4 Antitherapeutic Antibody (ATA)

The ATA incidence rate is defined as the proportion of subjects that develop ATA at any time during the study.

ATA incidence will be summarized by visit and overall using the safety analysis set.

7.7.5 Pharmacodynamic and Pre-treatment Biomarkers

The H-score of Nectin-4 expression at baseline will be summarized with descriptive statistics. Baseline H-score will be displayed in a boxplot by BOR. The number and percentage of subjects with baseline PD-L1 CPS <1 vs. ≥1, and <10 vs. ≥10 will be summarized. The TCGA subtype at baseline will be summarized. Additional analyses for pharmacodynamic biomarkers and for pre-treatment biomarkers that are potentially predictive of subject outcomes may be described in a separate analysis plan and the results may be reported separately from the CSR.

8 INTERIM ANALYSIS

Data from Cohort 2 will be analyzed at the timepoints as specified in Sect 6.10.

An IDMC will periodically monitor the trial for safety. The IDMC will review expedited SAEs as they are received. Further details will be provided in the IDMC Charter.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Original Protocol

Not Applicable.

9.2 Changes from the Original SAP

9.2.1 Version 2 Changes

The SAP was updated to reflect changes in protocol amendments 3, 4 and 5, and add additional details to the analysis. Changes from version 1 are summarized below:

- Sec 2.1, 4, 5, 6.1, 6.2 and 6.10: update per protocol amendments 3, 4 and 5

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- Sec 5.3: add efficacy evaluable set for sensitivity analysis of the primary efficacy endpoint
- Sec 6.4.3: update response assessment date algorithm following Paules 2011
- Sec 6.4.5: add data handling rule for action taken with study treatment of AE
- Sec 6.5 and Appendix C and D: add missing data handling rules for prior therapy and subsequent anticancer therapy dates
- Sec 6.8: update subgroup analysis to those based on important prognostic factors, and clarify subgroup analysis will not be performed for Cohort 2 at the time of the primary analysis of Cohort 1
- Sec 7.2: add summary of pre-existing conditions
- Sec 7.4: update algorithm for duration of treatment
- Sec 7.5.1 and 7.5.2: add definition for time to response; add waterfall plot for maximum percent reduction in sum of diameters
- Sec 7.5.2.1: add analysis to evaluate the concordance between investigator and IRF assessments
- Sec 7.6.1: update AE summary to base on treatment-emergent events only
- Sec 7.6.1.1: add additional details to the analysis of AESI
- Sec 7.6.1.2: add analysis for slit lamp examinations
- Sec 7.6.2: add summary of treatment-emergent laboratory abnormalities
- Sec 7.6.2.1: add liver safety assessment
- Sec 7.6.3: add summary of ECG parameters
- Sec 7.7: move Patient Reported Outcomes, Pharmacokinetics, ATA, and Biomarkers endpoints to 'Additional Analyses' section
- Sec 7.7.3: add summary of geometric mean ratio of drug product manufacturing process for selected PK parameters
- Sec 7.7.5: add summary of PD-L1 CPS and TCGA subtype
- Appendix B: update TEAE algorithm to better reflect the definition of TEAEs

9.2.2 Version 3 Changes

The SAP was updated to reflect changes in protocol amendment 6. Changes from version 2 are summarized below:

- Sec 5.3: updated the definition of 'efficacy-evaluable set' to allow adequate follow up for response related endpoints at the time of interim analyses

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- Sec 6.2 and 6.10: clarified the timing of Cohort 2 analyses and added additional interim analysis for Cohort 2 after approximately 70 subjects have been followed for approximately 8 months from the first dose of study drug

9.2.3 Version 4 Changes

Changes from version 3 are summarized below:

- Corrected section numbing for 6.4.3, 6.4.4, and 6.4.5
- Sec 6.8: clarified the number of subjects required in a subgroup to enable the subgroup analysis
- Sec 10: removed the references that were not cited in the SAP
- Appendix B: added additional details to the TEAE definition to account for changes in seriousness or relatedness for events that continue from the baseline conditions

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APPENDIX A: IMPUTATION OF PARTIAL MISSING ADVERSE EVENT DATES

The algorithm below should be used to impute pre-existing condition and adverse event (AE) start dates for which only partial information is known. For ease of reading, both pre-existing conditions and AEs will be referred to as AE for the remainder of this document. The algorithm should be applied to every AE record on a record by record basis. AE start dates should be imputed before imputation of AE condition end date in all cases. The AE condition end date should only be used in the imputation of the AE start date if it is a complete, known date.

AE day and month are missing

- If the year is the same as the year of first dose of study treatment and the onset period and/or onset time indicate that the start of the AE was pre-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of study treatment)
- If the year is the same as the year of first dose of study treatment and the onset period and/or onset time indicate that the start of the AE was post-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, first dose date of study treatment)
- If the year is before the year of first dose of study treatment:
  - AE start date will be imputed as the minimum of (AE condition end date*, December 31st see example 2 below)
- If the year is after the year of first dose of study treatment:
  - AE start date will be imputed as the minimum of (AE condition end date*, January 31st see example 2 below)

AE month only is missing

- Treat day as missing and replace both month and day according to the above procedure

AE day only is missing

- If the month/year is the same as the month/year of first dose of study treatment and the onset period and/or onset time indicate that the start of the AE was pre-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of study treatment)
- If the month/year is the same as the month/year of first dose of study treatment and the onset period and/or onset time indicate that the start of the AE was post-dose:
  - AE start date will be imputed as the minimum of (AE condition end date*, first dose date of study treatment)
- If the month/year is before the month/year of first dose of study treatment:

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- AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

- If the month/year is after the month/year of first dose of study treatment:
  - AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

* Only use condition end date if known and complete end date is available.

The following algorithm should be used to impute AE condition end dates. The AE records for a condition/event should be sorted by the imputed start dates then record position (order of entry into the eCRF). After sorting, if any condition end date month/year is greater than any subsequent record end date month/year, then change the imputed start day only to end of month. Repeat as necessary.

After sorting the AE records, apply the following rules to partial or missing AE condition end dates:

For all records excluding the last chronological record for a condition/event

- AE condition end date will be imputed as the start date of the subsequent record

For the last chronological record for a condition/event

- If outcome is "recovered/resolved", "recovered/resolved with sequelae", or "fatal" apply the following:
  - If only year is provided for the end date and year is equal to the year of the last dose date:
    - AE condition end date will be imputed as the minimum of (last dose date+30, death date, data extraction date, December 31st of the end date year)
  - If only year is provided for the end date and year is not equal to the year of the last dose date:
    - AE condition end date will be imputed as the minimum of (death date, data extraction date, December 31st of the end date year)
  - If month and year are provided for the end date:
    - AE condition end date will be imputed as the minimum of (death date, data extraction date, last day of the end date month/year)
- If outcome is "recovering/resolving", "not recovered/resolved", "unknown", or blank:
  - AE condition end date will not be imputed.

Example 1

AESPID 1: Condition/Event HEADACHE
First dose date 01JAN2012

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Prior to imputation

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	15APR2012	1	not recovered/resolved	pre-ICF
15APR2012	UNMAY2012	2	recovering/resolving	post 1st dose
UNMAY2012	UNJUN2012	1	not recovered/resolved	post 1st dose
UNJUN2012	UNJUN2012	3	recovering/resolving	post 1st dose
UNJUN2012	10JUL2012	2	recovering/resolving	post 1st dose
10JUL2012	--	1	not recovered/resolved	post 1st dose

Post imputation

Start date	Condition end date	Severity	Outcome
31DEC2011	15APR2012	1	not recovered/resolved
15APR2012	31MAY2012	2	recovering/resolving
31MAY2012	30JUN2012	1	not recovered/resolved
30JUN2012	30JUN2012	3	recovering/resolving
30JUN2012	10JUL2012	2	recovering/resolving
10JUL2012	--	1	not recovered/resolved

Example 2 (highlights choice of last day of the month as opposed to the 1st or the 15th)

AESPID 4: Condition/Event NAUSEA
First dose date 01APR2012

Prior to imputation

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	25APR2012	1	not recovered/resolved	pre-ICF
25APR2012	UNAPR2012	2	recovering/resolving	post 1st dose
UNAPR2012	04MAY2012	1	recovered/resolved	post 1st dose

Post imputation

Start date	Condition end date	Severity	Outcome
31DEC2011	25APR2012	1	not recovered/resolved
25APR2012	31APR2012	2	recovering/resolving
31APR2012	04MAY2012	1	recovered/resolved

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APPENDIX B: DEFINITION OF THE TERM "TREATMENT-EMERGENT" WITH RESPECT TO AE CLASSIFICATION

The algorithm below should be used to determine whether an adverse event (AE) is classified as a treatment-emergent adverse event (TEAE). A TEAE is defined as any AE which is newly occurring or worsening in severity, where newly occurring means that the AE was not present at baseline. For ease of reading, both pre-existing conditions and AEs will be referred to as AEs for the remainder of this document. AE dates should be imputed in accordance with the algorithm detailed in Appendix A prior to determination of TEAE classification. Details of the TEAE classification are as follows:

- For each subject, determine the first dose date, which is the earliest date the subject receives any amount of study drug.
- **Baseline AEs:** classify an AE record as baseline AE if it satisfies both criteria a and b below:

  a AE onset satisfies either of i, ii or iii below:
  - i. Onset date is prior to the first dose date
  - ii. Onset date is the same as the first dose date, and Onset Period is "started after consent but before the first dose of any study treatment" or Onset Time Relative to Study Treatment is "started before first infusion or before infusion on any dosing day"
  - iii. Onset Period is "started before the signing of consent" or "started after consent but before the first dose of any study treatment"

  b AE end date satisfies either of i or ii below:
  - i. End date is the same as or after the first dose date
  - ii. End date is missing with outcome equal to
    - recovering/resolving, or
    - not recovered/not resolved, or
    - unknown or missing

- **Post-baseline AEs:** classify an AE record as post-baseline AE if it meets either of criteria a, b or c below:

  a Onset date is after the first dose date

  b Onset date is the same as the first dose date, and Onset Period is "started after the first dose of any study treatment" or Onset Time Relative to Study Treatment is not "started before first infusion or before infusion on any dosing day"

  c Onset Period is "started after the first dose of any study treatment"

  Note: at interim timepoint, if an AE is classified as both 'baseline AE' and 'post-baseline AE' due to data issues, the AE is to be considered 'post-baseline AE' in the derivation of TEAE flag.

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- **TEAE flag** will be derived as follows:

  a. For all AE records that have an end date prior to the first dose date, assign TEAE flag to 'N'

  b. For all baseline AEs, assign TEAE flag to 'N'

  c. For post-baseline AEs where onset date is ≤30 days after last dose of study drug:

  - If the post-baseline AE is a continuing event of a baseline AE (i.e., events with the same AE identifier, where AE identifier is the number before the colon in SDTM AE.AESPID), then compare the CTCAE grade of the post-baseline AE to the CTCAE grade of the most recent baseline AE with the same AE identifier:
    - If the post-baseline AE has a higher CTCAE grade, then assign TEAE flag to 'Y'. All subsequent episodes of the same AE should have TEAE flag = 'Y' regardless of the CTCAE grade. If the CTCAE grade of the baseline AE is missing, then assign TEAE flag to 'Y'.
    - Else if the relationship to study drug changes from 'unrelated' to 'related' post-baseline, then assign TEAE flag to 'Y'.
    - Else if the seriousness of the AE changes from 'No' to 'Yes' post-baseline, then assign TEAE flag to 'Y'.
    - Otherwise, assign TEAE flag to 'N'
  - If the post-baseline AE is not a continuing event of a baseline AE, then assign TEAE flag to 'Y'

NOTE:

- **For summaries which include only treatment emergent AEs include all AEs which are classified as TEAEs as well as those AEs for which TEAE status could not be determined (e.g., the value of the TEAE variable may be missing if the event cannot be identified as baseline or post-baseline - missing information on the AE CRF should be queried). Only exclude those AEs which were determined to not be treatment emergent.**

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APPENDIX C: IMPUTATION OF PARTIAL MISSING PRIOR THERAPY DATES

Prior therapy dates will be imputed if both month and year are present and only day is missing.

- For prior therapy start date, impute the first day of the month.
- For prior therapy end date, impute the last day of the month or 14 days before the first dose of study drug, whichever is earlier.
- For date of progression on prior therapy, impute the last day of the month or the day before study enrollment, whichever is earlier.

After imputation rules are applied, use the following algorithm to determine if a prior therapy is to be included in the analysis:

- For CPI:
    - Include all therapies in locally advanced/metastatic setting.
    - Include all therapies in neo-adjuvant/adjuvant setting that reason off therapy is PD or the best response to the therapy is PD.
    - Include all therapies in neo-adjuvant/adjuvant setting that date of progression or date of locally advanced/metastatic disease is within 3 months after therapy completion.
- For platinum-based therapy:
    - Include all therapies in locally advanced/metastatic setting.
    - Include all therapies in neo-adjuvant/adjuvant setting that reason off therapy is PD or the best response to the therapy is PD.
    - Include all therapies in neo-adjuvant/adjuvant setting that date of progression or date of locally advanced/metastatic disease is within 12 months after therapy completion.
        - If month is missing for either prior therapy end date or PD date but year is the same for both dates, include the therapy in the analysis.
- For non-CPI/non-platinum based therapy:
    - Include all therapies indicated as given in locally advanced/metastatic setting with the exception of intravesical treatment.

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APPENDIX D: IMPUTATION OF PARTIAL MISSING SUBSEQUENT ANTICANCER THERAPY START DATE

Subsequent anticancer therapy start date will be imputed if both month and year are present and only day is missing.

- If the year of the subsequent anticancer therapy start date is the same as the year of the EOT date,
    - If the month of subsequent anticancer therapy start date is the same as the month of the EOT date, then the subsequent anticancer therapy start date will be imputed as the EOT date.
    - If the month of the subsequent anticancer therapy start date is later than the month of the EOT date, then the subsequent anticancer therapy start date will be imputed as the first day of the month.
    - If the month of the subsequent anticancer therapy start date is earlier than the month of the EOT date, then the subsequent anticancer therapy start date will be imputed as the last day of the month.
- If the year of the subsequent anticancer therapy start date is later than the year of the EOT date, then the subsequent anticancer therapy start date will be imputed as the first day of the month.

If the EOT date is missing, then the EOT date will be the end-of-study (EOS) date or 30 days after the last dose of any study drug, whichever is earlier.