Statistical Analysis Plan for Phase I/II Oncology Studies

Sponsor Name: Genmab

Protocol Number: GCT1046-01

Protocol Title: First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety of GEN1046 in subjects with malignant solid tumors.

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PPD

Author: PPD

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	02-Dec-2020	PPD	Initial Release Version. The SAP is considered stable so ADaM programming can begin. The following sections are considered stable: 2. Study Objectives 3. Study Design 4. Schedule of Assessments 6.1 Statistical and Analytical Issues 6.2.1 Subjects Disposition 6.2.2 Protocol Deviations 6.2.3 Background and Demographic Characteristics 6.2.4 Treatment Exposure 6.2.6 Medical Histories 6.3.1 Tumor Response (RECIST 1.1) 6.3.2.2 Progression Free Survival 6.3.2.3 Overall Survival 6.3.3 ECOG 6.4.1 Adverse Events 6.4.2 Physical Examination 6.4.3 Vital Signs 6.4.4 Electrocardiogram 6.4.5 Laboratory Parameters 6.10 Data Monitoring Committee 6.11 Changes to Methods Planned in the Protocol 7.1 Programming Guidelines 8. References
2.0	24-May-2023	PPD	Updated to include protocol amendments 4, 5, 6, 7, 8, 9 and 10 2.0 Modification of primary endpoint for EC1 as IRC assessment not performed (ORR instead of ORR with IRC assessment) 6.1.1 Specification of how cohorts and sub-cohorts will be presented 6.1.1.1 Clarification of on treatment period for safety summaries

I confirm that I have reviewed this document and agree with the content.

Approvals

Syneos Health Approval

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List of Abbreviations and Definition of Terms

Abbreviation or specialist term	Explanation
1Q3W or Q3W	Every 3 weeks
1Q6W or Q6W	Every 6 weeks
ADA	Anti-Drug Antibody
ADaM	Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guidelines
AE	Adverse Event
ALK	Anaplastic Lymphoma Kinase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BOR	Best Overall Response
CC	Cervical Cancer
CDISC	Clinical Data International Standards Consortium
CI	Confidence Interval
CPI	Check Point Inhibitor
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DDS	Dose Determining Set
DL	Dose Level
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	DeoxyriboNucleic Acid
DoR	Duration of Response
EC	Endometrial Cancer
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EC	Endothelial Carcinoma
EGFR	Epidermal Growth Factor Receptor
EoT	End of Trial
ER	Estrogen Receptor
EWOC	Escalation With Overdose Control
FAS	Full Analysis set
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FIH	First-in-human
HER2	Human Epidermal Growth Factor Receptor 2
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iCPD	immune Confirmed Progressive Disease

Abbreviation or specialist term	Explanation
iCR	immune Complete Response
iDCR	immune Disease Control Rate
iDoR	immune Duration of Response
iORR	immune Objective Response Rate
iPFS	immune Progression Free Survival
iPR	immune Partial Response
iRECIST	immune Response Evaluation Criteria in Solid Tumors
iSD	Immune Stable Disease
iUPD	immune Unconfirmed Progressive Disease
IHC	ImmunoHistoChemistry
HPV	Human PapillomaVirus
KM	Kaplan-Meier
KRAS	Kirsten RAt Sarcoma
mCRM	Modified Continual Reassessment Method
MedDRA	Medical Dictionary for Regulatory Activities
dMMR	Deficient Mismatch Repair
MTD	Maximum Tolerated Dose
MRI	Magnetic Resonance Imaging
MSI	MicroSatellite Instability
NCI	National Cancer Institute
NCS	Non Clinically Significant
NE	Not Evaluable
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PDc	Pharmacodynamic
PD-L1	Programmed Death-Ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PPoS	Predictive Probability of Success
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SI	Systeme Internationale
SOC	System Organ Class
Std	Standard Deviation
TEAE	Treatment-emergent adverse event
TLF	Tables, Listings and Figures
TNBC	Triple Negative Breast Cancer
UC	Urothelial Carcinoma
WHO	World Health Organization

1. Introduction

1.1 Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methods that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

1.2 Responsibilities

Syneos Health are responsible for the production and quality control of all disposition, demographic, baseline, efficacy and safety tables, listings and figures (TLFs). Pharmacokinetic (PK) and pharmacodynamic (PDc) and immunogenicity data also will be summarized by Syneos Health.

Genmab or a 3rd party vendor selected by Genmab are responsible for:

1) The adaptive design aspects of this study (maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) will be determined using a modified Continuous Reassessment Method (mCRM) and Escalation with Overdose Control (EWOC) design; and use of the predictive probability approach for futility analysis for each cohort in expansion phase.
2) Derivation of the PK parameters.
3) Analysis specifications of PK analyses beyond descriptive summaries and/or graphs planned for PK non compartmental analysis parameters and blood concentration of study drug (e.g. PK/Pharmacodynamic (PDc) modelling).

1.3 Timings of Analyses

Interim Analysis: Interim analysis for futility will be performed separately for each cohort (including subcohorts) after at least 10 subjects of a given cohort have been treated and had at least 1 response assessment post-baseline. An interim futility analysis will be conducted for Expansion Cohort (EC) 1 at ~12 weeks (ie, after second post-baseline tumor assessment) after the 40th subject is treated. Further details will be provided in SAP Section 6.8.

Final Analysis: The final analysis will be performed when all subjects have completed the expansion phase, i.e. when the last subject dies or withdraws from the trial. However, maximal trial duration is 3 years after the last subject's first treatment.

Data Monitoring Committee (DMC): The study conduct and safety of participants will be monitored by an independent DMC. The DMC will convene periodically in each study phase. Analysis specifications for those meetings are provided in a separate document (DMC TLFs Shells). See SAP Section 6.9.

2. Study Objectives

The study objectives and endpoints are described below in Tables 1 and 2.

Table 1. Objectives and Endpoints – Dose Escalation (All Cohorts), and Expansion Cohorts EC2-EC13

Objectives	Endpoints
Primary	
• Determine maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) • Establish safety profile of GEN1046	• Dose-limiting toxicity (DLT) • Adverse events (AEs) and safety laboratory parameters
Secondary	
• Evaluate the safety profile of GEN1046 in combination with docetaxel (EC9 only) • Evaluate the safety profile of GEN1046 in combination with pembrolizumab (1Q3W) (EC11a only) • Evaluate the safety profile of GEN1046 in combination with pembrolizumab (1Q6W) (EC11b only) • Evaluate the safety profile of GEN1046 in combination with pembrolizumab and platinum-based chemotherapy doublets (pemetrexed + cisplatin **OR** carboplatin [EC12 only]; carboplatin + paclitaxel **OR** nab-paclitaxel [EC13 only])	• AEs and safety laboratory parameters

• Characterize PK profile of GEN1046
• Evaluate immunogenicity of GEN1046
• Evaluate anti-tumor activity
	• PK parameters
	• Anti-Drug Antibody (ADA) response
	• Anti-tumor activity, ie, reduction in tumor size according to RECIST 1.1:
	  • Objective Response Rate (ORR)
	  • Disease Control Rate (DCR)
	  • Duration of Response (DoR)

Exploratory	
• To assess pharmacodynamics and potential biomarkers of GEN1046 • To assess anti-tumor activity based on iRECIST • Evaluate efficacy	• Immune system activation (eg, immune subset shift, tumor immune cell infiltration etc) • Anti-tumor activity, ie, reduction in tumor size according to iRECIST • iORR • Progression-free survival (PFS) • Overall survival (OS)

1Q3W=1 dose every 3 weeks; 1Q6W=1 dose every 6 weeks; EC=expansion cohort; iORR=immune objective response rate; iRECIST=immune Response Evaluation Criteria in Solid Tumors; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors.

Table 2. Objectives and Endpoints – Expansion Cohort EC1

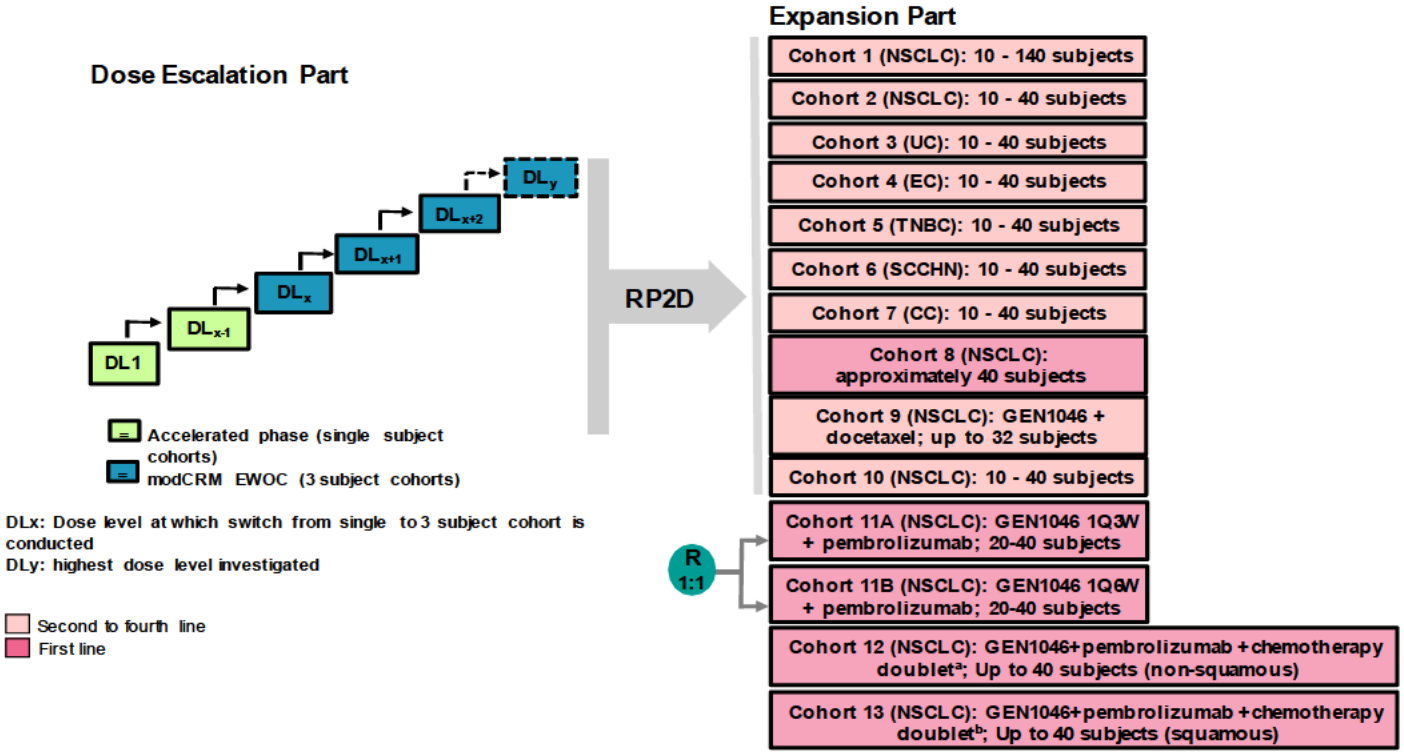
Objectives	**Endpoints**
Primary	
• Evaluate clinical efficacy	• Objective Response Rate per RECIST 1.1 (ORR)
Secondary	
• Evaluate the safety profile of GEN1046	• Adverse events (AEs) and safety laboratory parameters
• Further evaluate clinical efficacy	• DoR, PFS per RECIST 1.1 • Overall survival (OS)
• Characterize PK and immunogenicity of GEN1046	• PK parameters • Anti-Drug Antibody (ADA) response
Exploratory	
• To assess pharmacodynamics and potential biomarkers of GEN1046	• Immune system activation (eg, immune subset shift, tumor immune cell infiltration etc)
• To assess anti-tumor activity based on iRECIST	• Anti-tumor activity, ie, reduction in tumor size according to iRECIST • iORR

EC=expansion cohort; iORR=immune objective response rate; iRECIST=immune Response Evaluation Criteria in Solid Tumors; PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors.

3. Study Design

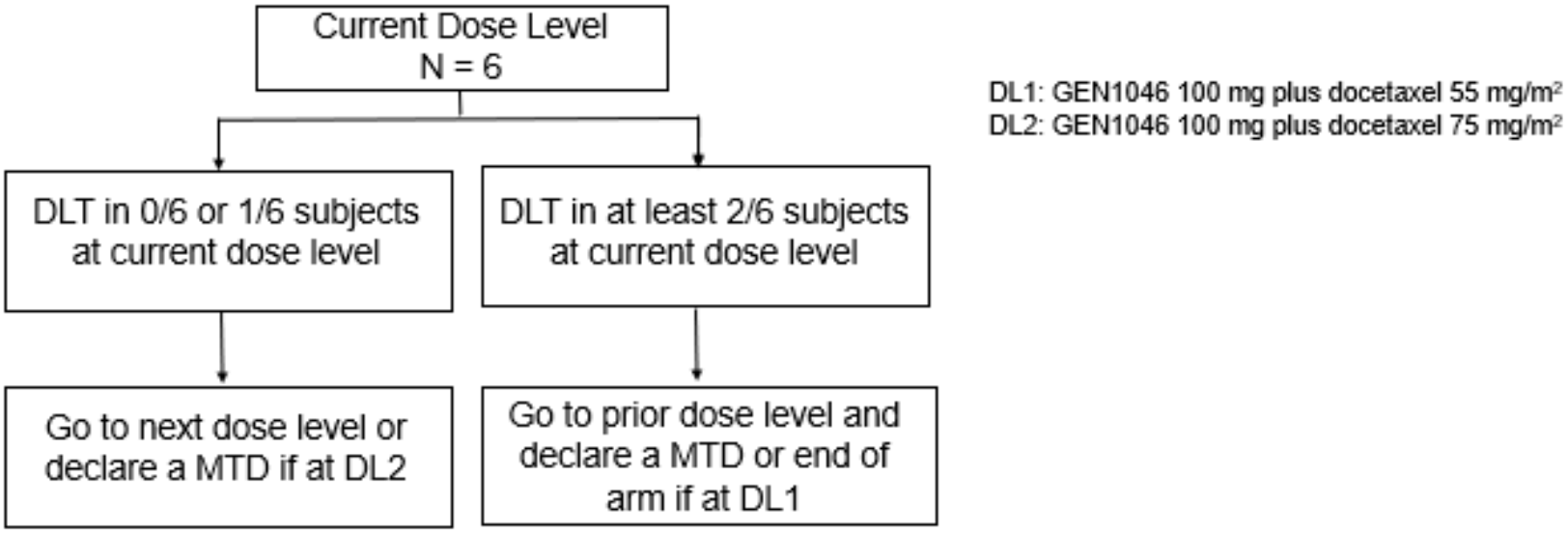
This is an open-label, multi-center, phase 1/2a safety trial of GEN1046 (DuoBody®-PD-L1×4-1BB). The trial consists of 2 consecutive parts: a first-in-human (FIH) dose escalation (phase 1) and an expansion (phase 2a).

Figure 1. Overview of Trial Design



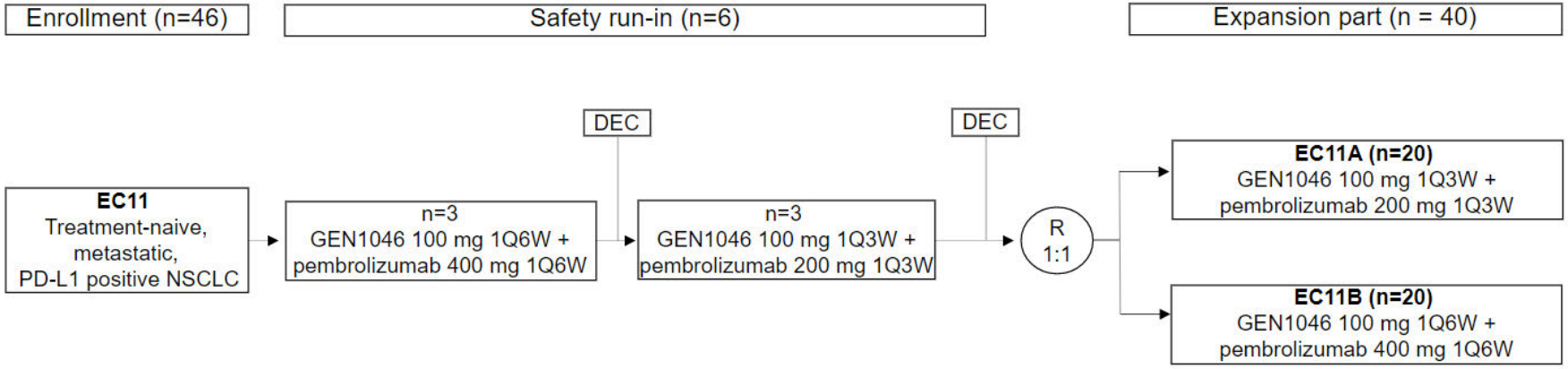
1Q3W = once (1 dose) every 3 weeks; 1Q6W = once (1 dose) every 6 weeks; CC = cervical cancer; EC = endometrial cancer; NSCLC = non-small cell lung cancer; RP2D = recommended phase 2 dose; SCCHN = squamous cell carcinoma of the head and neck; TNBC = triple-negative breast cancer; UC = urothelial carcinoma.
a The platinum-based chemotherapy doublet for EC12 is pemetrexed + cisplatin **OR** carboplatin.
b The platinum-based chemotherapy doublet for EC13 is carboplatin + paclitaxel **OR** nab-paclitaxel.

Figure 2. Safety Run-In Escalation Design – EC9 – Docetaxel Combination



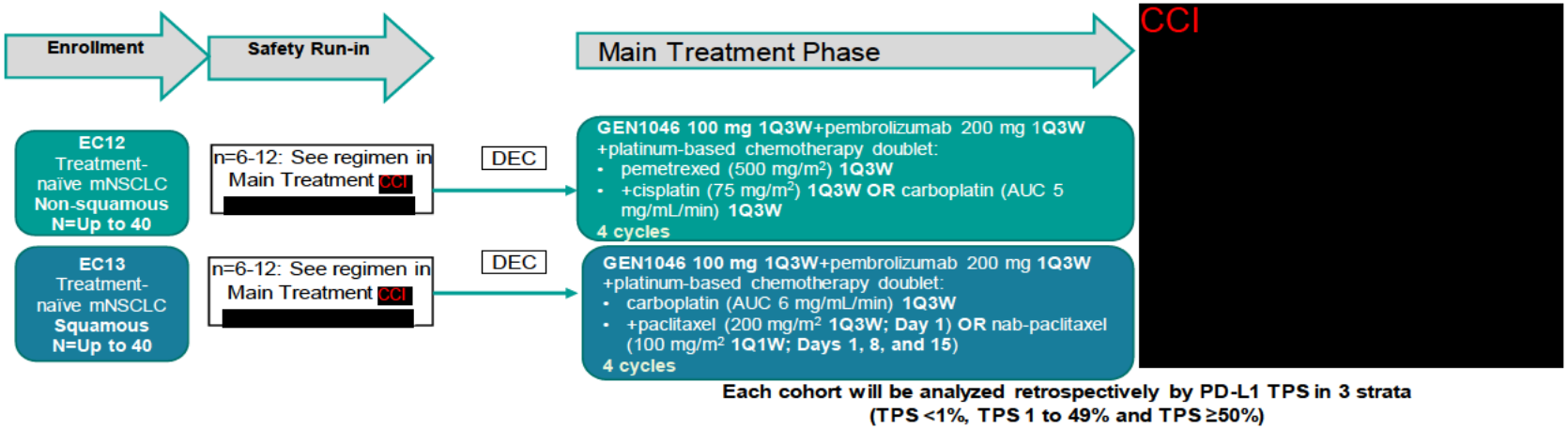
DL = dose level; DLT = dose-limiting toxicity; EC = expansion cohort; MTD = maximum tolerated dose.

Figure 3. Safety Run-In – EC11 – Pembrolizumab Combination



1Q3W = once (1 dose) every 3 weeks; 1Q6W = once (1 dose) every 6 weeks; DEC = dose escalation committee; NSCLC = non-small cell lung cancer; R = randomization.

Figure 4. Detailed Schema Including Safety Run-in for Expansion Cohorts EC12 and EC13 – Pembrolizumab Combination with Chemotherapy Doublets



1Q1W = once (1 dose) every week; 1Q3W = once (1 dose) every 3 weeks; DEC = dose escalation committee; mNSCLC = metastatic non-small cell lung cancer.

Table 3. Expansion Cohorts

Cohort No.	n	Cancer Type	Subcohort	Prior Treatment	Trial Treatment
EC1	Up to 140	NSCLC	N/A	Prior CPI treatment	GEN1046 100 mg 1Q3W
EC2	40	NSCLC	N/A	PD-1/L1 inhibitor-naive	GEN1046 100 mg 1Q3W
EC3	40	UC	EC3a (platinum eligible)	Prior CPI treatment	GEN1046 100 mg 1Q3W
			EC3b (platinum ineligible)	Prior CPI treatment	GEN1046 100 mg 1Q3W
EC4	40	Endometrial cancer	N/A	PD-1/L1 inhibitor-naive	GEN1046 100 mg 1Q3W
EC5	40	TNBC	5a	Prior CPI treatment	GEN1046 100 mg 1Q3W
			5b	PD-1/L1 inhibitor-naive	GEN1046 100 mg 1Q3W
EC6	40	SCCHN	6a	Prior CPI treatment	GEN1046 100 mg 1Q3W
			6b	PD-1/L1 inhibitor-naive	GEN1046 100 mg 1Q3W
EC7	40	Cervical cancer	N/A	PD-1/L1 inhibitor-naive	GEN1046 100 mg 1Q3W
EC8	40	NSCLC	8a (PD-L1 + low [TPS 1% to 49% or 1% to 49% TC])	No prior treatment for metastatic disease	GEN1046 100 mg 1Q3W × 2 cycles; then GEN1046 500 mg 1Q6W for remaining cycles
			8b(PD-L1 + high [TPS ≥50% or ≥50% TC])	No prior treatment for metastatic disease	GEN1046 100 mg 1Q3W × 2 cycles; then GEN1046 500 mg 1Q6W for remaining cycles
EC9 (Docetaxel Combination)	32	NSCLC	N/A	Prior CPI treatment; no prior docetaxel treatment	DL1: GEN1046 100 mg 1Q3W and docetaxel 55 mg/m^2 1Q3W DL2: GEN1046 100 mg 1Q3W and docetaxel 75 mg/m^2 1Q3W

Cohort No.	n	Cancer Type	Subcohort	Prior Treatment	Trial Treatment
EC10 (prior to amendment 5)	40	NSCLC	N/A	Prior CPI treatment	GEN1046 100 mg 1Q3W × 2 cycles; then GEN1046 500 mg 1Q6W for remaining cycles
EC10 (after amendment 5)	40 minus the number of subjects enrolled prior to amendment 5	NSCLC PD-L1+ (TPS ≥1%)	N/A	Prior CPI treatment	GEN1046 100 mg 1Q3W × 2 cycles; then GEN1046 500 mg 1Q6W for remaining cycles
EC11a (pembrolizumab combination)	Up to 40	NSCLC PD-L1+ (TPS ≥1% or ≥1% TC)	N/A	No prior treatment for metastatic disease	GEN1046 100 mg 1Q3W and pembrolizumab 200 mg 1Q3W
EC11b (pembrolizumab combination)	Up to 40	NSCLC PD-L1+ (TPS ≥1% or ≥1% TC)	N/A	No prior treatment for metastatic disease	GEN1046 100 mg 1Q6W and pembrolizumab 400 mg 1Q6W
EC12 (non-squamous; in combination with pembrolizumab and platinum-based chemotherapy doublet)	Up to 40	NSCLC PD-L1 status: All comers	N/A	No prior treatment for metastatic disease	**Main Treatment Phase (4 cycles):** GEN1046 100 mg 1Q3W + pembrolizumab 200 mg 1Q3W + pemetrexed (500 mg/m^2) 1Q3W + cisplatin (75 mg/m^2) 1Q3W **OR** carboplatin (AUC 5 mg/mL/min) 1Q3W CCI [redacted]

Cohort No.	n	Cancer Type	Subcohort	Prior Treatment	Trial Treatment
EC13 (squamous; in combination with pembrolizumab and platinum-based chemotherapy doublet)	Up to 40	NSCLC PD-L1 status: All comers	N/A	No prior treatment for metastatic disease	**Main Treatment Phase (4 cycles):** GEN1046 100 mg 1Q3W + pembrolizumab 200 mg 1Q3W + carboplatin (AUC 6 mg/mL/min) 1Q3W + paclitaxel (200 mg/m^2) 1Q3W (Day 1) **OR** nab-paclitaxel (100 mg/m^2) 1Q1W (Days 1, 8, and 15) CCI [redacted]

1Q1W = once (1 dose) every week; 1Q3W = once (1 dose) every 3 weeks; 1Q6W= once (1 dose) every 6 weeks; AUC = area under the curve; CPI=checkpoint inhibitor; DL=dose level; EC=expansion cohort; N/A = not applicable; NSCLC=non-small cell lung cancer; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; SCCHN=squamous cell carcinoma of the head and neck; TC=tumor cells for CCI [redacted] Assay scoring algorithm; TNBC=triple-negative breast cancer; TPS=tumor proportion score (for CCI [redacted] scoring algorithm); UC=urothelial carcinoma.

The dose escalation evaluates GEN1046 in subjects with solid malignant tumors to determine the MTD or maximum administered dose and/or the RP2D. The expansion further evaluates the safety, tolerability, PK, and anti-tumor activity of the selected dose(s) in select solid tumors.

Approximately 725 subjects can be enrolled in the trial. Assuming an anticipated screen failure rate of 30%, approximately 943 subjects can be screened.

Approximately 100 subjects were planned to be enrolled in the dose escalation. A total of 61 subjects had been enrolled when enrollment in the dose escalation part was completed.

Approximately 652 subjects are planned to be enrolled in the expansion (380 subjects in cohorts EC1 to EC7, 40 subjects in EC8, 32 subjects in EC9 [the docetaxel combination], 40 subjects in EC10, and up to 80 subjects in EC11 [the pembrolizumab combination], and up to 80 subjects in EC12 and EC13 combined [GEN1046+pembrolizumab+platinum-based chemotherapy doublets; including the safety run-in]). 372 subjects had been enrolled at the time of Protocol Version 10 (Protocol Amendment 8.0) release.

4. Schedule of Assessments

The schedule of assessments is described in Protocol Section 1.

5. Analysis Populations

The Full Analysis Set (FAS), which consists of all subjects enrolled and treated with at least one dose of GEN1046 (or any study drug for the combination therapy subjects), will be used for safety, efficacy, PK and PDc analyses. The per protocol set will not be applicable. Note Protocol Section 11.5 refers to a 'safety set'. Typically, this set is defined as any subject enrolled and receiving at least one dose of study drug. This is the definition of the FAS therefore 'safety set' and 'FAS' are synonymous. 'FAS' will be used throughout this SAP and the TLFs.

The Dose-Determining Set (DDS) consists of all subjects from the FAS who meet the minimum exposure criterion for Cycle 1 and have either completed the DLT observation period, or have experienced a DLT during Cycle 1. A subject is considered to have met the minimum exposure criterion at a dose level if GEN1046 has been administered for at least 90% of the planned dose in each of the infusions. Subjects who do not experience DLT during the first cycle are considered to have sufficient safety evaluations if they have been observed for minimum 21 days following the first dose, and are considered to have enough safety data to conclude that a DLT did not occur. This constitutes all evaluable subjects for the determination of MTD. The DDS used in the Bayesian framework of the mCRM with EWOC design in dose escalating phase, will not apply to analyses produced by Syneos Health and, as a result, will not be presented in the analyses.

6. Statistical Methodology

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

Tabulations will be produced for appropriate demographic, baseline, efficacy, safety, PK, PDc and immunogenicity parameters. Each phase, dose escalation and dose expansion, will be presented

separately. Unless otherwise specified, summaries will be presented by escalating planned dose level for Cycle 1 for the dose escalation and a 'Total' column; and by expansion cohort for expansion and a 'Total' column.

EC8 will be analyzed in 2 strata. These are captured in the eCRF as 'EC8a' (NSCLC PD-L1 + low [TPS 1% to 49% or 1% to 49% TC]) and 'EC8b' (NSCLC PD-L1 + high [TPS >= 50% or >=50% TC]). 'EC8a' and 'EC8b' will be used to differentiate the 2 different strata throughout this SAP and in the TLFs.

For expansion disposition, baseline characteristics and efficacy output, column headers will be ordered:

EC1
EC2
EC3a
EC3b
EC4
EC5a
EC5b
EC6a
EC6b
EC7
EC8a
EC8b
EC9
EC10
EC11a
EC11b
EC12
EC13

A 'Total' column is not required for efficacy related output.

For expansion safety output, column headers will be ordered:

EC1+2
EC3a+3b
EC4
EC5a+5b
EC6a+6b
EC7
EC1-7
EC8a
EC8b
EC9
EC10
EC11a
EC11b
EC12
EC13
Total

Note safety run-in data for EC9, EC11, EC12 and EC13 will not be summarized separately. See TLF shells for further details.

Only the first (earliest) assessment of multiple assessments on the same day (planned, repeat) will be included in summary tables unless specified otherwise, but all assessments will be included in the listings. If multiple pre-treatment assessments, the last (closest to Cycle 1 Day 1) will be used for baseline.

In general, unscheduled visit data will be listed but not included in the summary tables by visit/time point. Unscheduled data will be included to identify the worst case post-baseline on-treatment value for safety tables.

Continuous variables will be summarized by reporting the number of observations, mean, standard deviation, median, minimum, and maximum out output over 3 lines as follows:

n
mean (std)
median (min, max)

Categorical variables will be summarized using frequency tables showing the number and percentage of subjects within a particular category, where the denominator is N. A 'Missing' row will be added where appropriate (unless otherwise specified).

By-subject data listings will be produced for data collected through the study. All data listings that contain an evaluation date will contain a relative study day (Study Day). Study days are numbered relative to the day of the first dose of study drug, which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc.

Unless otherwise specified, listings will be sorted by phase: escalating dose level for dose escalation and EC number for expansion. Within each phase, listings will be sorted by cohort, subject number (enrollment ID) and assessment date/time. Screen failure data will not be listed.

Missing records will be omitted from the listings, and missing data within a record will be left blank. 'Not Done' records will be summarized as such and will not be counted as 'missing'.

Time to event data will be analyzed using Kaplan-Meier survival estimates and censored in accordance with the Food and Drug Administration (FDA) Guidance: "Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics". Summary statistics will include median, 25th, and 75th percentile survival times (as available) and corresponding 95% confidence intervals (CIs).

As this is a Phase 1/2 trial, formal statistical hypothesis testing will not be performed. Although exploratory CIs will be presented, these data will be used for exploratory purposes only.

Statistical analyses will be carried out by using SAS Version 9.4 or higher. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the clinical study report.

Analysis datasets used for statistical analyses will be developed according to CDISC (Clinical Data Interchange Standards Consortium) Analysis Data Model (ADaM) Version 2.1 corresponding to Version 1.1 of the Analysis Data Model Implementation Guide (ADaMIG). Documentation (DEFINE.xml and Analysis Data Reviewer's Guide) will be provided.

Adverse events will be graded by the Investigator based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, and will be coded for summarization using the Medical Dictionary for Regulatory Activities (latest effective MedDRA® Version). Concomitant medications and prior/new systemic anti-cancer treatments will be coded using the World Health Organization (WHO) Drug Dictionary (latest effective version).

6.1.1.1 Key Definitions

'Study drug' is GEN1046 for monotherapy and GEN1046 or any other study drug for combination expansion cohorts:

1. EC9 - GEN1046 or docetaxel
2. EC11a/EC11b – GEN1046 and/or pembrolizumab
3. EC12 - GEN1046, pembrolizumab, pemetrexed, cisplatin and/or carboplatin
4. EC13 - GEN1046, pembrolizumab, carboplatin, paclitaxel and/or nab-paclitaxel

Study day is the day relative to the date of first dose of study drug where Day 1 is the first day of any study drug.

There are 3 analysis periods within the study as follows:

1. Pre-treatment: < first dose date and time of any study drug.
2. On-treatment: >= first dose date and time of any study drug to earliest of (<=last study drug dose date and time + 60 days or start of new anti-cancer treatment or withdrawal of consent or death (whichever comes first)).
3. Post-treatment > last dose date and time of any study drug + 60 days.

The analysis periods will be used for adverse event and medication summaries.

Additional treatment periods for adverse event summaries for EC10, EC12 and EC13 are as follows:

1. EC10 (GEN1046 Monotherapy)
    a. Activation phase (GEN1046 100 mg 1Q3W for 2 cycles): >= first dose date to < first dose date of 500 mg.
    b. CCI [redacted]
2. EC12 (Combination Therapy)
    a. Main Treatment Phase (4 cycles): >= first dose date of any study drug to <= last dose date of cisplatin or carboplatin.
    b. CCI [redacted]

3. EC13 (Combination Therapy)
    a. Main Treatment Phase (4 cycles): >= first dose date of any study drug to <= last dose date of carboplatin, paclitaxel or nab-paclitaxel.
    b. CCI [redacted]

The first dose date is defined as the first non-missing date where a non-zero dose of study drug was recorded.

The last dose date is defined as the last non-missing date where a non-zero dose of study drug was recorded.

Unless otherwise specified, baseline is the last non-missing observation before the start of any study drug, which is expected to be Day 1 of Cycle 1 (pre-dose), or screening if the Day 1 data are not available.

6.1.1.2 Visit Windows

All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window.

6.1.2 Handling of Subjects Discontinuing the Trial, Missing Data and Partial Dates

Missing data will be treated as missing and no data will be imputed except for:

- Adverse events where relationship to study drug is missing (see SAP Section 6.4.2)
- Certain critical dates as described below in Table 4

Table 4. Imputation for Partial or Missing Critical Dates

Date	Day (or Start Time or End Time) Missing	Day and Month Missing	Completely Missing
Death Date[1]	MAX (last day of contact, 01-Mmm-yyyy)	MAX (last day of contact, 01-Jan-yyyy)	Last day of contact. However, should never occur.
Start Date New Anti-cancer Therapy, Radiotherapy and Surgery	Impute as maximum of last dose date and last RECIST response assessment + 1 day if the month and year are the same as the last dose date or the last RECIST response assessment, otherwise set day to '01-Mmm-yyyy'.	Impute as maximum of last dose date and last RECIST response assessment + 1 day.	No imputation.
Diagnosis and Prior Systemic Anticancer Therapy, Radiotherapy and Surgery Dates:	Impute as '01-mmm-yyyy'	Impute '01-Jul-yyyy'. If year same as first dose date, impute '01-Jan-yyyy'	No imputation.
Adverse Events Start Dates (and Times) [1]	MAX (first dose date, 01-Mmm-yyyy) Impute 00:00 if start date is after first dose date. Impute first dose start time if start date is same as first dose date Impute first dose date if year and month are equal to first dose date. Otherwise impute '01'.	MAX (first dose date, 01-Jan-yyyy)	First dose date.
Adverse Events End Dates[2]	LL-Mmm-yyyy, where LL is last day of the month. Missing AE end times will not be imputed.	31-Dec-yyyy	
RECIST Assessment date when outcome is PD, SD[1] , [3]	MAX(first dose date, 01-Mmm-yyyy)	MAX(first dose date, 01-Jan-yyy)	No imputation. However, should never occur
RECIST Assessment date when outcome is CR, PR[3]	LL-Mmm-yyyy, where LL is last day of month	31-Dec-yyyy	No imputation. However, should never occur

[1] MAX=maximum of.
[2] Consideration will be taken with partial end dates with missing days, to ensure that months having differing number of days are taken into account. Special consideration will be applied with February because of the extra day included in leap years.
[3] Tumor assessment per RECIST1.1/iRECIST.

No imputation of incomplete or missing dates for any other historical data will be done.

Assigning Adverse Events to Analysis Periods (SAP Section 6.1.1.1)

An AE will be assumed to be treatment emergent if it cannot be definitively shown that the AE did not occur or worsen during the on-treatment period (worst case approach). The following general rules will be used:

- If the start day is missing but the start month and year are complete, an AE will be excluded as being treatment-emergent only if the start month/year is before the month/year of study product administration or if the stop date/time is before study product administration.
- If the start day and month are missing but the start year is complete, an AE will be excluded as being treatment-emergent only if the start year is before the year of study product administration or if the stop date/time is before study product administration.
- If the start date is completely missing, an AE will be considered treatment-emergent unless the stop date is before study product administration.

Assigning Medications to Analysis Periods (SAP Section 6.1.1.1)

Medications missing both start and stop dates or having a start date prior to the first dose of any study drug and missing the stop date, or having a stop date on or after the last dose of any study drug and missing start date will be counted as concomitant.

For partial dates, the following approach will be taken:

- If the start day is missing but the start month and year are complete, a medication will be excluded as being concomitant only if the start month/year is before the month/year of any study drug administration and if the stop date (either full date, month and year if missing day, or year if missing month and day) is before any study drug administration.
- If the start day and month are missing but the start year is complete, a medication will be excluded as concomitant only if the start year is before the year of any study drug administration and if the stop date (either: full date, month and year if missing day, or year if missing month and day) is before any study drug administration.

SAP Section 6.3.1.2 describes censoring rules for time-to-event endpoints.

6.1.3 Pooling of Investigative Sites

As this is a Phase 1/2a study, no by-site analyses are planned.

6.1.4 Determination of Sample Size

Dose Escalation: Approximately 100 subjects are expected to be included in the dose-escalation. Operational characteristics for the Bayesian CRM are provided in Protocol Appendix 2 and Appendix 3.

Expansion: 380 subjects in cohorts EC1 to EC7, 40 subjects in EC8, 32 subjects in EC9 [the docetaxel combination], 40 subjects in EC10, and up to 80 subjects in EC11 [the pembrolizumab combination], and up to 80 subjects in EC12 and EC13 combined [GEN1046+pembrolizumab+platinum-based

chemotherapy doublets; including the safety run-in]) are planned. Maximal total sample size of the expansion is expected to be approximately 652 subjects.

The null hypothesis is that the ORR for the EC1 subject population is at most 15%, and the alternative hypothesis is that the ORR is at least 30%. With 1 sample binomial test, a sample size of 140 subjects will provide 97% power to reject the null hypothesis with a 2-sided significance level of 0.05. The probability of futility with 40 evaluable subjects is 60.7% under the null hypothesis and 2.4% under the alternative hypothesis.

6.2 Subject Characteristics

6.2.1 Subject Disposition

All subjects will be used. The table will include the 'Subjects ongoing with treatment' defined as exposed subjects with no 'End of Treatment' page populated in the eCRF; similarly, the table will include the 'Subjects ongoing in the study' defined as exposed subjects with no 'End of Study' page populated in the eCRF.

Tabulation will include the following:

- Number (%) eligible.
- Number (%) eligible subjects not treated and reason for not moving into treatment phase.
- Number (%) enrolled and treated (FAS).
- Number (%) of subjects ongoing with treatment, who discontinued GEN1046 treatment and the primary reason for discontinuation.
- Number (%) of subjects ongoing with treatment, who discontinued docetaxel treatment and the primary reason for discontinuation. EC9 only.
- Number (%) of subjects ongoing with treatment, who discontinued pembrolizumab treatment and the primary reason for discontinuation. EC11, EC12 and EC13 only.
- Number (%) of subjects ongoing with treatment, who discontinued pemetrexed treatment and the primary reason for discontinuation. EC12 only.
- Number (%) of subjects ongoing with treatment, who discontinued cisplatin treatment and the primary reason for discontinuation. EC12 only.
- Number (%) of subjects ongoing with treatment, who discontinued carboplatin treatment and the primary reason for discontinuation. EC12 and EC13 only.
- Number (%) of subjects ongoing with treatment, who discontinued paclitaxel treatment and the primary reason for discontinuation. EC13 only.
- Number (%) of subjects ongoing with treatment, who discontinued nab-paclitaxel treatment and the primary reason for discontinuation. EC13 only.

- Number (%) of subjects ongoing in the study, withdrawing from the study and the primary reason for withdrawal.

6.2.2 Protocol Deviations

Deviations will be managed as detailed in Protocol Deviation and Non-compliance Management Plan.

There is no per-protocol analysis planned for this study.

Important protocol deviations will be summarized for the FAS. The details of all deviations will be listed. Important deviations are a subset of major deviations and will be determined based on project team review. A separate summary and listing for COVID-19 related protocol deviations will be provided.

6.2.3 Background and Demographic Characteristics

Demographic and baseline disease characteristics will be presented for the FAS. The following demographic variables will be summarized using both continuous and categorical descriptive statistics:

- Age (years)
- Age group (< 65 years, >= 65 years)
- Sex (Male, Female. Including child bearing potential for female subjects Yes, No)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2)
- Geographic Region (US, EU, Other)
- Tobacco use (Never, Current, Former)
- Alcohol use (Never, Current, Former)

BMI is derived as weight (kg) / $[height\ (m)]^2$.

The following disease characteristics variables will be summarized:

- Time since initial cancer diagnosis (months), calculated as the date of first dose minus date of initial diagnosis divided by 30.4375. See SAP Section 6.1.2 which details how to deal with partial dates.
- Time since metastatic disease diagnosis (months), calculated as the date of first dose minus date of metastatic disease diagnosis divided by 30.4375. See SAP Section 6.1.2 which details how to deal with partial dates.
- Time since most recent progression (months), calculated as the date of first dose administration minus date of progression (from 'Prior Systemic Anti-cancer Therapy eCRF' divided by 30.4375).
- Cancer type (NSCLC, TNBC, SCCHN, Cervical Cancer, Endometrial Cancer, Urothelial Cancer, Other).
- Cancer Type (reclassified for 'Other'. Applies to dose escalation only). See Table 5 below.
- Cancer Stage
- T, N and M Status
- Disease Status at Study Entry (Locally Advanced, Metastatic)

- Prior lines of systemic anti-cancer therapy (0, 1, 2, 3, 4, >=5), mean, median and range in metastatic or locally advanced settings. For EC1, EC2 and EC10 only a metastatic setting applies, not both. For all other ECs, both settings apply.
- Sites of disease at screening (Liver, Brain, Bone, Lymph Nodes)
- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, >=2)
- Prior CPI (Yes, No)
- Prior anti-cancer surgery (Yes, No)
- Prior radiation therapy (Yes, No)

Cancer Type (reclassified): in the dose escalation phase (enrollment completed on 4th of May 2020), cancer types reported in 5 or more patients exposed in the dose escalation phase will be grouped into categories created from cancer type initially pre-defined in the eCRF (data field "cancer type") if not "Other", and the details captured as free-text field (data field "If other, specify") for other types of cancer as summarized below. Note this table will be updated following cleaning of the escalation phase data.

Table 5. Reclassified Cancer Type.

Cancer type (as reported into CRF)	**If Other, specify (as reported in the eCRF)**	**Cancer Type (reclassified)**
Non-Small Cell Lung Cancer (NSCLC)		NSCLC
Other	COLORECTAL CANCER, Colorectal Cancer, Colorectal cancer, colorectal cancer or colon cancer	Colorectal Cancer
Other	OVARIAN CANCER, Ovarian Cancer, Ovarian adenocarcinoma, Ovarian cancer, ovarian cancer	Ovarian Cancer
Other	PANCREATIC CANCER, Pancreatic Cancer, pancreatic cancer	Pancreatic Cancer
Other combinations		Other

A separate table for each cancer type will also be provided summarizing disease status variables as follows:

NSCLC

- PD-L1 status (assessed centrally)
- PD-L1 status (assessed locally)
- Histology results
- EGFR mutation
- ALK rearrangement status
- ROS1 status
- KRAS

TNBC

- PD-L1 status (assessed centrally)
- PD-L1 status (assessed locally)
- Histology results
- HER2 status
- ER status
- PgR ('PR' in the CRF) status
- MSI/dMMR status

SCCHN

- PD-L1 status (assessed centrally)
- PD-L1 status (assessed locally)
- HPV status
- EGRF status

Cervical

- PD-L1 status (assessed centrally)
- PD-L1 status (assessed locally)
- Histology results
- FIGO stage
- HPV status
- MSI/dMMR status

Endometrial

- PD-L1 status (assessed centrally)
- PD-L1 status (assessed locally)
- Histology results
- FIGO stage
- MSI/dMMR status

Urothelial; Other types

- PD-L1 status (assessed centrally)
- PD-L1 status (assessed locally)

Archival tumor sample data will be listed using the FAS.

6.2.4 Medications and Therapies

Prior and Subsequent Systemic Cancer Therapy

The FAS will be used. Prior systemic regimens in a metastatic or locally advanced setting combined will be summarized separately. A summary of prior systemic anti-cancer therapies across settings will also be summarized using Anatomical Therapeutic Chemical (ATC)1/ATC4 and active ingredient as described below for concomitant medications. A summary of subsequent anti-cancer therapies across all settings by ATC1/ATC4 and active ingredient will also be provided.

All prior (pre-treatment) and subsequent (post-treatment) systemic anti-cancer therapies will be listed by phase, cohort and subject number and therapy start date. SAP Section 6.1.2 describes how to handle partial dates.

Prior and Concomitant Medications

The FAS will be used. SAP Section 6.1.1.1 describes the analysis periods. Prior medication will be defined as any medication taken prior to the first dose of any study drug (pre-treatment period). Concomitant medication is defined as any medication taken during the on-treatment period. Any medications taken after on-treatment period will be considered as post-treatment medications. Medications can only be classified in one of the three analysis periods. SAP Section 6.1.2 describes how to handle partial dates.

Concomitant medications will be presented in tabular form using ATC classification system level 1 (main anatomical/pharmacological group), ATC level 4 (chemical subgroup) and active ingredient. All medications will be sorted by descending frequency within the 'Total' column at ATC level 1 and then, within ATC level 1, by descending frequency of ATC level 4 and then within ATC level 4 by decreasing frequency of active ingredient. If incidence for more than 1 term is identical, they will be sorted alphabetically. The number and percentage of subjects who took at least one medication within each specific ATC level 4 will be presented. Subjects will only be counted once if they are taking more than one medication or take the same medication more than once. Section 6.2.4 of the protocol details the excluded prior and concomitant medications.

All prior (pre-treatment), concomitant, and post-treatment medications will be listed by phase, cohort, subject number and medication start date.

Other Therapy

Prior surgery for the disease type studied in the trial before informed consent was signed will be listed by phase, subject and surgery date. Similarly, prior radiotherapy will be listed by phase, subject and radiotherapy start date. New anti-cancer surgery and new anticancer radiotherapy will also be listed in the same way.

6.2.5 Medical Histories

The FAS will be used. Medical history will be coded by using the MedDRA latest version. Medical history frequencies will be ordered by descending frequency within the 'Total' column by SOC then, within a SOC, by overall descending frequency of PT. If the incidence for more than 1 term is identical, they will be sorted alphabetically. Medical history will be listed by phase, cohort, subject number and start date.

6.3 Efficacy Analysis

Descriptive statistics on efficacy will be presented by dose level for dose escalation and cohort for expansion using the FAS, unless otherwise noted.

Please see SAP Section 2. Efficacy endpoints are either secondary or exploratory as detailed in the sections below.

6.3.1 Tumor Response (RECIST 1.1)

Tumor response will be assessed according to RECIST 1.1 (Eisenhauer et al, 2009) by the investigator according to the schedule of assessments (on-trial imaging will be performed at Week 6 (±7 days), every 6 weeks (±7 days) for 50 weeks, and every 12 weeks (±7 days) thereafter from the date of first dose until disease progression is assessed by the investigator, the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts. If imaging shows progressive disease (PD), then a subsequent imaging assessment should be performed within at least 4 weeks to confirm progression.

Missing assessments will not be imputed.

Objective Response Rate (ORR)

Confirmed ORR per RECIST 1.1 by the investigator is defined as proportion of subjects with a best overall response (Complete Response (CR) or Partial Response (PR)) confirmed by a subsequent best overall response of CR or PR at least four weeks later.

Table 6 Definition of Response (RECIST Criteria 1.1)

	Category	**Criteria**
Based on target lesions	Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to < 10 mm.
	Partial Response (PR)	≥ 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of longest diameters.
	Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while in trial. Follow-up measurements must have met the SD criteria at least once and for a minimum time period of 5 weeks after first treatment.
	Progressive Disease (PD)	≥ 20% (and ≥ 5 mm) increase in the sum of the diameters of target lesions, taking as reference the smallest sum of the target diameters recorded while in trial or the appearance of 1 or more new lesions.
Based on non-target lesions	CR	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
	SD	Persistence of 1 or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
	PD	Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions.

The best overall response is the best response recorded from the start of the treatment until PD/recurrence (the smallest measurements recorded since the treatment started will be used as the reference for PD).

Confirmed best overall response is derived per RECIST 1.1 as follows:

Table 7 Best Overall Response when Confirmation of CR or PR required

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

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

The frequency distribution of individual confirmed best overall response (CR, PR, SD, and PD) and the confirmed objective response rate (defined as CR+PR)/all eligible subjects x 100 will be presented. ORR including unconfirmed responders will also be summarized in separate tables.

Subjects for which response cannot be ascertained will be assumed to have no response and will be considered non-responders in the analysis. Subjects without a post-baseline tumor assessment will also be considered non-responders. Appendix 1 describes in further detail how best overall response will be assigned programmatically. An exact unadjusted 95% CI, calculated using the Clopper-Pearson method (Clopper and Pearson, 1934), will be included.

Disease Control Rate (DCR)

DCR will be summarized as described above for objective response rate. DCR is defined as CR+PR+SD/ all eligible subjects x 100. 95% CI will be included.

Reduction in Target Lesions

A waterfall plot for best percentage change from baseline in the sum of target lesion longest diameters will be provided by dose level for dose escalation and cohort for expansion. The Y axis will be percent change from baseline and subject number on the X axis. A positive result indicates an increase in tumor size; a negative result indicates a decrease (shrinkage). The best response (CR, PR, SD, PD and NE) requiring confirmation of CR or PR. will be included. Unconfirmed CR or PR will be recorded as SD if the minimum criteria for SD duration has been met, otherwise NE (as described in Table 7).

The RECIST 1.1 target lesion measurements, non-target lesion status and new lesion as collected on the eCRF will be listed separately by phase, cohort, subject number and evaluation date.

Duration of Response

DOR only applies to subjects whose confirmed best overall response is CR or PR and is defined as time from the first documentation of objective tumor response (CR or PR) to the date of first PD or death.

DOR (months) = [(Date of progression/death – date of first PR/CR) + 1] / 30.4375

DOR will be censored and summarized as described for PFS in SAP Section 6.3.1.2.

Exploratory Efficacy Analysis

6.3.1.1 Tumor Response (iRECIST)

iRECIST is based on RECIST 1.1 but has been modified to account for the unique response patterns observed with immunotherapy (Seymour et al., 2017).

iRECIST disease progression should be confirmed at least 4 weeks after the first radiologic evidence of PD in clinically stable participants. Subjects who have unconfirmed disease progression may continue on study treatment until progression is confirmed as long as the subject is clinically stable as described is Protocol Section 9.2.1.

Responses assigned using iRECIST have a prefix of “i” e.g., “immune” complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for stable disease (iSD), disease control rate (iDCR) and objective response rate (iORR).

The iRECIST endpoints are analyzed using the same statistical methodology and the results presented in the same way as for the corresponding RECIST 1.1 ones, *e.g.*, iORR should be analyzed and reported in the same way as ORR, see SAP Section 6.3.1 above for details.

If too few responders are observed (i.e. the difference between RECIST 1.1 and iRECIST, ORR vs. iORR) or there are too few subjects beyond RECIST 1.1 PD, this exploratory analysis may be omitted and a listing will be provided instead.

6.3.1.2 Progression Free Survival

PFS is defined as the time from Day 1 in Cycle 1 to the first documented progression or death due to any cause.

PFS will be censored as described in Table 8.

If a subject has no post-baseline tumor assessment, PFS will be censored at study drug first dose date.

These rules are summarized in the Table 8 below.

Table 8. Censoring Rules. (FDA guideline on Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. FDA April 2015. Based on Table D1):

Situation	Date of Progression or Censoring [1]	Outcome
Incomplete or no baseline tumor assessments	Date of first dose	Censored
Progression documented between scheduled visits	Date of progression assessment	Progressed
No progression	Date of last visit with adequate assessment	Censored
New anti-cancer treatment started	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed tumor assessment. [2]	Date of last visit with adequate assessment [3]	Censored

[1] Progression is assessed radiologically.
[2] This includes NE visits.
[3] Prior to the missing assessments.
Note: an 'adequate assessment' is defined as an assessment where response is CR, PR or SD, i.e. not NE.

PFS will be derived for all subjects and presented graphically as well as summarized using survival analysis methods.

The quartile estimates of PFS from the Kaplan Meier (Kaplan & Meier, 1958) product limit algorithm will be presented. The 2-sided 95% confidence interval will be presented as well.

The date of first dose, disease progression, death, last tumor assessment and date of last contact and PFS days will be listed by phase, cohort and subject number.

6.3.1.3 Overall Survival

OS is defined as time from Day 1 in Cycle 1 to death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).

OS will only be analyzed for the expansion using the same techniques and presented in the same manner as PFS (SAP Section 6.3.1.2).

Subjects lacking data beyond the day of the first dose will have their survival times censored at the date of the first dose with duration of 1 day.

OS data will be reported with the PFS data as described in SAP Section 6.3.1.2.

Follow up time (months), calculated as the date of last contact a subject is known to be alive minus date of first dose of study drug + 1 divided by 30.4375, will be summarized.

6.3.2 Evaluation of Performance Status

The FAS will be used.

A summary table will be provided with the number and percentage of subjects by performance status at each visit. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). If there are multiple results at a given visit, the earliest value will be used in the tables (see SAP Section 6.1).

Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) data will be listed by phase, cohort, subject number and assessment date.

6.3.3 Tumor Biopsy

Levels of intra-tumoral biomarkers will be associated with efficacy responses for the expansion cohorts EC1-EC13 from fresh and/or archival biopsies at baseline as well as biopsies after treatment initiation, subject to availability. For example, responder vs. non-responder could be evaluated vs. biomarker value via box and whisker plots as appropriate depending on the final data.

For baseline, both archival and fresh tumor biopsy meta data will be described with the following:

1. Time since last biopsy to start date of GEN1046 study drug (months): ([Date of first study drug GEN1046 dose – date of last biopsy] + 1) / 30.4375.
2. No. of subjects with archival biopsies vs. fresh biopsies.

For biopsies obtained after treatment initiation, tumor biopsy meta data will be described with the number of subjects where biopsies taken by visit. Note the tumor biopsy/tissue sampling schedule is different for EC8, EC10, EC11, EC12 and EC13. See Protocol Section 1.3.3 for details.

Further summaries may be considered, and details provided in a separate document.

6.4 Safety Analysis

The FAS will be used.

Unless otherwise specified, summary tables will be produced for results within the on-treatment period as described in SAP Section 6.1.1.1.

For combination therapy (EC9 docetaxel; EC11 pembrolizumab; EC12 and EC13 pembrolizumab/ chemotherapeutic combination agent), first dose and last dose refer to any study drug, i.e. GEN1046, docetaxel, pembrolizumab or chemotherapeutic combination agent.

The safety assessment schedule can be different for expansion cohorts. See protocol section 1.3 for details.

6.4.1 Treatment Exposure

Monotherapy

GEN1046 exposure will be presented cumulatively by dose level for dose escalation and by cohort for expansion (EC1-EC8 separately, EC10) using the FAS. Note for EC10, in the ADaMs ADEX and ADEXSUM, the parameters described below will be derived overall and by treatment phase as described in SAP Section 6.1.1.1.

The following variables will be presented overall (not by cycle):

1. Duration of exposure (months): ([the earliest of the following: date of last infusion + 20 days, last contact date, death date, data cutoff date) – date of first infusion + 1) x 12/365.25
2. The number of doses received will be summarized using both continuous and categorical descriptive statistics.
3. The total cumulative dose (mg) received ('Total dose administered (mg)' in eCRF).
4. Actual dose Intensity (mg/cycle). Computed as the ratio of total cumulative dose received and duration of exposure. For EC8 and EC10, actual dose intensity will be calculated separately for cycle 1 and 2 as well as the actual dose intensity from cycle 3 onwards.
5. Relative dose intensity (%) = 100*actual dose intensity / (planned dose intensity). For EC1 – EC7 the planned dose intensity is 100 mg/3 weeks. For EC8 and EC10, planned dose intensity will be is 100mg/3 weeks for cycle 1 and 2 and 500mg/6 weeks from cycle 3 onwards.
6. Infusion interruptions and dose adjustments. A subject is only counted once. If there are any interruptions or adjustments, a subject will be counted as 'Yes'. The number of interruptions and adjustments per subject will also be summarized. The categories are '0', '1', '2', '>2'. These categories maybe revised based on the distribution of the final data.

Combination Therapy (EC9, EC11a, EC11b, EC12 and EC13)

GEN1046, docetaxel, pembrolizumab, pemetrexed, cisplatin, carboplatin, paclitaxel and nab-paclitaxel exposure will be presented cumulatively for combination therapy expansion cohorts EC9, EC11a, EC11b, EC12 and EC13 using the FAS.

The combination therapies are summarized below:

EC9 (Docetaxel Combination)	Dose Level 1: GEN1046 100 mg 1Q3W and docetaxel 55 mg/m^2 1Q3W Dose Level 2: GEN1046 100 mg 1Q3W and docetaxel 75 mg/m^2 1Q3W
EC11a (GEN1046 in combination with pembrolizumab)	GEN1046 100 mg 1Q3W and pembrolizumab 200 mg 1Q3W
EC11b (GEN1046 in combination with pembrolizumab)	GEN1046 100 mg 1Q6W and pembrolizumab 400 mg 1Q6W
EC12 (non-squamous; GEN1046 in combination with pembrolizumab and platinum-based chemotherapy doublet)	**Main Treatment Phase (4 cycles):** GEN1046 100 mg 1Q3W + pembrolizumab 200 mg 1Q3W + pemetrexed (500 mg/m^2) 1Q3W + cisplatin (75 mg/m^2) 1Q3W **OR** carboplatin (AUC 5 mg/mL/min) 1Q3W CCI [redacted]
EC13 (squamous; GEN1046 in combination with pembrolizumab and platinum-based chemotherapy doublet)	**Main Treatment Phase (4 cycles):** GEN1046 100 mg 1Q3W + pembrolizumab 200 mg 1Q3W + carboplatin (AUC 6 mg/mL/min) 1Q3W + paclitaxel (200 mg/m^2) 1Q3W (Day 1) **OR** nab-paclitaxel (100 mg/m^2) 1Q1W (Days 1, 8, and 15) CCI [redacted]

Exposure to each study drug will be presented separately.

Note for EC12 and EC13, in the ADaMs ADEX and ADEXSUM, the parameters described below will be derived overall and by treatment phase as described in SAP section 6.1.1.1.

The following variables will be presented overall (not by cycle):

1. Duration of exposure (months): ([the earliest of the following: date of last infusion + planned length of last cycle, last contact date, death date, data cutoff date) – date of first infusion + 1) x 12/365.25. Planned length of last cycle:
    a. EC9. GEN1046 and docetaxel - 21 days.
    b. EC11a. GEN1046 and pembrolizumab - 21 days.
    c. EC11b. GEN1046 and pembrolizumab - 42 days.
    d. EC12. GEN1046, pembrolizumab, pemetrexed, cisplatin and carboplatin – 21 days
    e. EC13. GEN1046, pembrolizumab, carboplatin, paclitaxel and nab-paclitaxel – 21 days
2. The number of doses received will be summarized using both continuous and categorical descriptive statistics.
3. The total cumulative dose (mg) received ('Total dose administered (mg)' in eCRF). Units will be mg/m2 for docetaxel, pemetrexed, cisplatin, paclitaxel and nab-paclitaxel and mg/mL/min for carboplatin.
4. Actual dose Intensity. Computed as the ratio of total cumulative dose received and duration of exposure. Units as follows:
    a. EC9
        i. GEN1046 - mg/3 weeks.
        ii. Docetaxel - mg/m^2/3 weeks
    b. EC11a. GEN1046 and pembrolizumab - mg/3 weeks.
    c. EC11b. GEN1046 and pembrolizumab - mg/6 weeks.
    d. EC12
        i. GEN1046 and pembrolizumab - mg/3 weeks.
        ii. Pemetrexed and cisplatin - mg/m^2/3 weeks
        iii. Carboplatin – AUC mg/mL/min/3 weeks
    e. EC13
        i. GEN1046 and pembrolizumab - mg/3 weeks.
        ii. Carboplatin – AUC mg/mL/min/3 weeks
        iii. Paclitaxel and nab-paclitaxel - mg/m^2/3 weeks

5. Relative dose intensity (%) = 100*actual dose intensity / (planned dose intensity). Planned dose intensity:
    a. EC9
        i. GEN1046 - 100 mg/3 weeks
        ii. Docetaxel Dose Level 1 - 55 mg/m^2/3 weeks
        iii. Docetaxel Dose Level 2 - 75 mg/m^2/3 weeks
    b. EC11a
        i. GEN1046 – 100 mg/3 weeks
        ii. Pembrolizumab 200 mg/3 weeks.
    c. EC11b
        i. GEN1046 – 100 mg/6 weeks
        ii. Pembrolizumab 400 mg/6 weeks.
    d. EC12
        i. GEN1046 – 100 mg/3 weeks
        ii. Pembrolizumab – 200 mg/3 weeks.
        iii. Pemetrexed – 500 mg/m2/3 weeks
        iv. Cisplatin – 75 mg/m^2/3 weeks
        v. Carboplatin – 5 mg/mL/min/3 weeks
    e. EC13
        i. GEN1046 – 100 mg/3 weeks
        ii. Pembrolizumab – 200 mg/3 weeks.
        iii. Carboplatin – 6 mg/mL/min/3 weeks
        iv. Paclitaxel – 200 mg/m^2/3 weeks
        v. Nab-paclitaxel – 300 mg/m^2/3 weeks (100 mg/m^2 administered on Days 1, 8 and 15)
6. Infusion interruptions and dose adjustments. A subject is only counted once. If there are any interruptions or adjustments, a subject will be counted as ‘Yes’. The number of interruptions and adjustments per subject will also be summarized. The categories are ‘0’, ‘1’, ‘2’, ‘>2’. These categories maybe revised based on the distribution of the final data.
7. The number of subjects where GEN1046, docetaxel, pembrolizumab, pemetrexed, cisplatin, carboplatin, paclitaxel and nab-paclitaxel was permanently discontinued will be summarized.
8. Duration of exposure of each study drug will be presented by cohort and subject in a swimlane plot.

All administration data will be listed by phase, cohort and subject number.

6.4.2 Adverse Events

AEs will be graded according to the NCI CTCAE Version 5.0, coded using the MedDRA coding system (latest effective version), and displayed in tables and data listings by SOC and preferred term PT.

Summary tables for AEs will include only AEs that are treatment-emergent. Treatment emergence is any AE that started or worsened during the on-treatment period (see SAP Section 6.1.1.1).

Additional treatment periods for adverse event summaries for EC10 (activation vs. CCI [redacted] are described in SAP Section 6.1.1.1 Treatment emergent flags will be derived overall and for each treatment period resulting in 3 sets of treatment emergent flags.

SAP Section 6.1.2 details how to handle partial dates to determine treatment emergence.

The incidence of TEAEs will be summarized by SOC and or PT, severity (CTCAE grade), type of AE and relationship to GEN1046 or any study drug ('Related' indicates related to GEN1046 and/or any other study drug). A subject contributes only once to the count for a given SOC or PT (i.e., the most related occurrence or the most intense occurrence). Tables will be presented by alphabetically by SOC and then, within a SOC, by descending frequency of PT within the 'Total' column.

Missing relationship will be considered related to study drug.

SAEs and AEs during the on-treatment period will be tabulated.

All deaths (on treatment and post treatment) will be summarized by cause of death.

All AEs, deaths, SAEs (including those from the pre- and post-treatment periods), TEAEs leading to discontinuation of study drug and DLTs (DLTs applies to dose escalation and safety run-in the expansion phase only) will be listed by phase, cohort and subject number and those collected during the pre-treatment and post-treatment period will be flagged. For EC10, activation vs. CCI [redacted] will be flagged and similarly for EC12 and EC13, CCI [redacted] will be flagged.

An overview table of on-treatment TEAEs will be produced and will include:

- The number and percentage of subjects reporting at least 1 TEAE
- The number and percentage of subjects reporting at least 1 related TEAE.
- The number and percentage of subjects reporting at least 1 serious AE (SAE)
- The number and percentage of subjects reporting at least 1 related serious TEAE.
- The number and percentage of subjects reporting at least 1 TEAE with toxicity grade of 3 or higher
- The number and percentage of subjects reporting at least 1 related TEAE with toxicity grade of 3 or higher.
- The number and percentage of subjects reporting a TEAE leading to treatment discontinuation.
- The number and percentage of subjects reporting a related TEAE leading to treatment discontinuation.
- The number and percentage of subjects reporting a fatal TEAE.

- The number and percentage of subjects reporting a related fatal TEAE.

The number and percentage of subjects reporting at least 1 TEAE classified as a DLT in Cycle 1 will also be included (dose escalation and safety run-in in the expansion phase only).

Tabulations by SOC and/or PT will be produced for:

- TEAEs by SOC and PT
- TEAEs by PT
- TEAEs with incidence rate >=10% by PT
- TEAEs by PT and maximum CTCAE grade
- Treatment related TEAEs by PT
- Treatment related TEAEs with incidence rate >=10% by PT
- Treatment related TEAEs by PT and maximum CTCAE grade
- TEAEs with grade >=3 by PT
- Treatment related TEAEs with grade >=3 by PT
- TEAEs resulting in treatment discontinuation by PT for GEN1046/docetaxel/pembrolizumab/pemetrexed/cisplatin/carboplatin/paclitaxel/nab-paclitaxel
- TEAEs resulting in dose interruption by PT for GEN1046/docetaxel/pembrolizumab/pemetrexed/cisplatin/carboplatin/paclitaxel/nab-paclitaxel
- TEAEs resulting in dose delay by PT for GEN1046/docetaxel/pembrolizumab/pemetrexed/cisplatin/carboplatin/paclitaxel/nab-paclitaxel
- TEAEs resulting in dose modification (dose reduction and/or drug interruption and/or dose delay) for GEN1046/docetaxel/pembrolizumab/pemetrexed/cisplatin/carboplatin/paclitaxel/nab-paclitaxel
- Treatment emergent SAEs by SOC and PT
- Treatment emergent SAEs by PT
- Treatment emergent SAEs with incidence rate >=2% by PT
- Treatment related treatment emergent SAEs by PT
- Grade 5 TEAEs by PT
- Summary of Common (>=10%) non-serious AEs by SOC and PT. Number of subjects and occurrences.
- Summary of SAEs by SOC and PT. Number of subjects and occurrences.

The above tables will be repeated for:

- EC10 comparing TEAEs during the CCI .
- EC12 and EC13 comparing TEAEs during the CCI .

To further investigate toxicity, specific PTs will be grouped according to Genmab, e.g. immune-mediated TEAEs. Details are provided in Appendix 2. Note the final list may change based on emerging data and will be finalized nearer to database lock. Only PTs included in a pre-defined Group will be included in the summaries. The incidence of TEAEs will be summarized by Group and PT as described above for SOC and PT. Tables will be presented by alphabetically by Group and then, within a Group, by descending frequency of PT within the 'Total' column.

Tabulations by Group and PT will be produced for:

- TEAEs by Group and PT
- Treatment related TEAEs by Group and PT
- TEAEs with grade >=3 by Group and PT
- TEAEs resulting in treatment discontinuation by Group and PT for GEN1046/docetaxel/pembrolizumab/pemetrexed/cisplatin/carboplatin/paclitaxel/nab-paclitaxel
- Treatment emergent SAEs by Group and PT
- Treatment related treatment emergent SAEs by Group and PT
- Grade 5 TEAEs by Group and PT

A separate listing of TEAEs alphabetically by Group, phase, cohort and subject number will be provided.

Related SAEs by PT will be presented for post-treatment AEs (AEs starting after the on-treatment period).

Data from SAE Supplemental Safety Reporting Forms 1 and 2 will not be listed.

6.4.3 Physical Examination

Physical examination assessments will be conducted. Clinically significant findings from the physical examinations will be reported as either medical history or AEs as applicable. Height is collected at Screening and will be listed with the demography data.

Abnormal Not Clinically Significant (NCS) and Abnormal Clinically Significant (CS) physical examination results will be listed by phase, cohort, subject number, date of examination and body system as per eCRF order.

6.4.4 Vital Signs

The following vital signs will be assessed as described in Protocol Section 1.3 (Schedule of Activities): systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min [bpm]), temperature (degrees C) and weight (kg).

Summary statistics for vital signs at each scheduled visit and time point and changes from baseline will be presented. Baseline is defined as the last non-missing assessment before the first dose of study drug. The baseline value is expected to be Day 1 pre-infusion. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). If there are multiple results at a given visit, the earliest value will be used in the tables (see SAP Section 6.1).

Note temperature will be reported in centigrade. Any conversions required will be as follows:

Temperature (in °Centigrade (C)) = 5/9 (Temperature [in °Fahrenheit (F)]-32).

Toxicity grading following the NCI CTCAE grades version 5.0 will be derived for vital signs where applicable (see table below). Note, where gradings require investigator/clinical input, this will not be considered and only the numeric criteria will be used for the assignments. CTCAE grade 0 will be assigned for all non-missing values not graded as 1 or higher.

Table 9 Gradable Vital Sign Parameters

Parameter	**NCI-CTCAE Term**
Systolic Blood Pressure	Hypertension
Diastolic Blood Pressure	Hypertension
Temperature	Fever
Weight	Weight gain
Weight	Weight loss

Heart rate is non-gradable. Heart rate results will be categorized as low (< 50 bpm)/normal (50-100 bpm)/high (> 100 bpm).

For vital signs where grades are defined by the CTCAE:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.

Only subjects with both a non-missing baseline and at least one non-missing post-baseline grade will be included in the shift tables. Unscheduled data will be included in the worst case across all scheduled and unscheduled visits after the first dose of study treatment. This means that if there are CTCAE grades derived from both unscheduled and scheduled visits data per test per subject then the highest on-treatment grade will be summarized.

For heart rate:

Shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment (see SAP Section 6.1.1.1) value.

Worst post-baseline high and worst post-baseline low will be summarized separately. Only subjects with both a non-missing baseline and at least one non-missing post-baseline grade will be included in the shift tables. The determination of the worst-case takes into account both planned and unscheduled assessments.

Vital signs will be provided in data listings by phase, cohort, subject number, assessment date/time and parameter.

6.4.5 Electrocardiogram (ECG)

The following ECG results will be assessed: PR interval (msec), QRS interval (msec), QT Interval (msec), QTcF Interval (msec) and RR interval (msec).

The ECGs will be recorded digitally at the sites by using the standard 12-leads. ECG assessments will be conducted as described in Protocol Section 1.3 (Schedule of Activities).

The digital ECGs will be transmitted from the sites electronically to a central laboratory for a measurement of the cardiac intervals and morphologic assessment by a central laboratory cardiologist.

An overall interpretation of the ECGs will be performed by the investigator, or a cardiologist, if applicable. The central reading will be used for analysis purposes. The local reading will be listed.

For the ECG recordings, the subjects must be resting and in a supine or reclined position for at least 10 minutes.

A summary table of PR, QRS, QT, QTcF and RR by visit/time point and change from baseline to visit/time point will be provided. Prior to summary, the mean of the 3 results (where triplicate readings were taken) will be determined per subject per visit/time point. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date and time point for which it was recorded (ie, no visit windows will be applied). If there are multiple results at a given visit/time point, eg a repeated ECG test within a visit/time point, the earliest value will be used in the tables (see SAP Section 6.1).

Central tendency analysis: the change from baseline in PR, QRS, QT, QTcF and RR will be summarized by visit/time point using descriptive statistics including standard deviation and 90% confidence intervals.

A CTCAE grade will be assigned (CTCAE term, 'Electrocardiogram QT corrected interval prolonged') to QTcF. A shift from baseline summary table of QTcF CTCAE grade to the worst (highest) value on study (based on individual assessment, not and aggregation of the triplicate readings). The determination of the worst-case post baseline takes into account both planned and unscheduled assessments. Patients with missing baseline values are assumed to have baseline value below the lowest threshold (i.e. less than 450 msec).

A summary table of the following will be presented by visit/time point:

- QTcF values > 450 msec and ≤ 480 msec; > 480 msec and < 500 msec; and ≥ 500 msec
- QTcF increase from baseline values ≥ 30 msec and <60 msec; and ≥ 60 msec
- QRS change from baseline > 25% resulting in QRS > 120 msec
- RR interval change from baseline >25% reaching a value >220 msec

All ECG parameters will be provided in data listings (where 'Overall Interpretation' is not 'Normal') by phase, cohort, subject number, assessment date and parameter (in the order PR, QRS, QT, QTcF and RR interval and overall interpretation).

A separate listing will be provided for subjects who had a treatment emergent NCI-CTCAE grade >= 1 for QTcF. treatment emergent is defined in SAP Section 6.1.1.1 All QTcF records per subject will be included in the listing.

6.4.6 Laboratory Parameters

Both local and central laboratories will be used for analysis of the tests detailed in Protocol Table 9-2 according to the visit schedules in Protocol Section 1.3 and summarized separately. Hematology, chemistry, endocrine, serum (beta-hCG) pregnancy and hepatitis B will be performed centrally. Coagulation factors, urine pregnancy and urinalysis will be performed locally.

The investigator must review all laboratory results (ie, from both central and local laboratories) and record any clinically relevant changes including dose modifications or delays as an AE.

Hematology, biochemistry, coagulation factors and endocrine parameters will be summarized in the order in the eCRF. All summaries will be based on results in Systeme Internationle (SI) units. High/low classifications will be derived relative to the result and normal range in SI units where normal ranges exist.

For hematology, biochemistry and coagulation summary tables by visit and change from baseline to visit for each laboratory parameter will be provided using local and central data; for endocrine data, only central laboratory data will be used. Coagulation data will be summarized with hematology data and endocrine data with the biochemistry data. Baseline is defined as the last non-missing assessment before the first dose of study drug. The baseline value is expected to be Day 1 pre-dose. Summaries will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). If there are multiple results at a given visit, the earliest value will be used in the tables (see SAP section 6.1).

The eCRF states that differential counts can be entered as 'Absolute' values OR 'Percentage' values. Percentage white blood cell (WBC) differential counts will be converted to absolute values. As each differential always adds up to 100%, the total WBC can be used to derive absolute values. For example, if a relative neutrophil value = 70% and the total WBC = 6.20 10^9/L, then the absolute neutrophil value = 4.34 10^9/L (0.7 x 6.20).

Grading of laboratory values will be assigned programmatically as per the NCI CTCAE v5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE grade 0 will be assigned for all non-missing values not graded as 1 or higher.

Table 10. CTCAE Gradable Parameters

Parameter Type	**Parameter**	**NCI-CTCAE Term**
Hematology	Platelets	Platelet count decreased
	Hemoglobin	Anemia
	Hemoglobin	Hemoglobin increased
	WBC	Leukocytosis
	WBC	White blood cell decreased
	Lymphocytes	Lymphocyte count decreased
	Neutrophils	Neutrophil count decreased
	Eosinophils	Eosinophilia
Biochemistry	Albumin	Albuminuria
	ALT	Alanine aminotransferase increased
	ALP	Alkaline phosphatase increased
	Amylase	Serum amylase increased
	AST	Aspartate aminotransferase increased
	Calcium	Hypercalcemia
	Calcium	Hypocalcemia
	Creatinine	Creatinine increased
	GFR Calculation	Chronic Kidney Disease
	Total bilirubin	Blood bilirubin increased
	Gamma-glutamyl Transferase	GGT Increased
	Glucose	Hypoglycemia
	Lactate dehydrogenase	Lactate dehydrogenase increased
	Lipase	Lipase increased
	Magnesium	Hypermagnesemia
	Magnesium	Hypomagnesemia
	Sodium	Hypernatremia
	Sodium	Hyponatremia
	Potassium	Hyperkalemia
	Potassium	Hypokalemia
Coagulation	INR	INR increased
	Activated partial thromboplastin time	Activated partial thromboplastin time prolonged

For laboratory tests where grades are not defined by the CTCAE, results will be categorized as low/normal/high based on laboratory normal ranges.

Table 11. Non-gradable Parameters

Parameter Type	**Parameter**
Hematology	RBC
	Hematocrit
	MCV
	MCH
	MCHC
	Reticulocytes
	Monocytes
	Basophils
Biochemistry	BUN
	Chloride
	C-reactive Protein
	Ferritin
	Glycosylated Hemoglobin
	Phosphate
	Total Protein
	Uric Acid
Endocrine	TSH
	Free T4
	Free T3

The following summaries will be generated separately for hematology, and biochemistry tests:

For laboratory tests where grades are defined by the CTCAE:

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.

Only subjects with both a non-missing baseline and at least one non-missing post-baseline grade will be included in the shift tables. Unscheduled data will be included in the worst case across all scheduled and unscheduled visits after the first dose of study treatment. This means that if there are CTCAE grades derived from both unscheduled and scheduled visits data per test per subject then the highest on-treatment grade will be summarized.

For laboratory tests where grades are not defined by the CTCAE:

Shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment (see SAP Section 6.1.1.1) value.

Worst post-baseline high and worst post-baseline low will be summarized separately for bi-directional parameters. Only subjects with both a non-missing baseline and at least one non-missing post-baseline grade will be included in the shift tables. The determination of the worst-case takes into account both planned and unscheduled assessments. Only laboratory tests which cannot be graded per CTCAE v. 5.0 specified criteria will be included.

A plot of the mean and standard error of each local laboratory result will be displayed graphically over time. The x axis will be scheduled visit.

All abnormal laboratory results (i.e. values not within the standard reference range for central data and not within the original range for local data) in original and SI units will be included in data listings by source (local then central), phase, cohort, subject number, assessment date and using the parameter order in the eCRF.

Urinalysis results will be listed.

6.5 Pharmacokinetic Analysis

GEN1046 concentration data will be summarized and may be explored graphically using a mean concentration time plot for cycle 1, 2. Values below limit of quantification will be counted as having a value of half the lower limit of quantification.

GEN1046 concentration data will be listed.

Further evaluation of PK may be presented in a separate report as per protocol section 11.7.

6.6 Pharmacodynamic Analysis

Biomarkers will be summarized by timepoint using descriptive statistics. Any pharmacodynamic measures will be listed, tabulated and plotted as appropriate.

6.7 Immunogenicity

As GEN1046 is a PD-L1x4-1BB bispecific antibody, a potential ADA can develop against the PD-L1 arm, the 4-1BB arm or both. Hence, a subject can be considered positive or negative for each of the following: ADAs targeting the PD-L1 arm (irrespective of targeting the 4-1BB arm), ADAs targeting the 4-1BB arm (irrespective of targeting the PD-L1 arm) as well as ADAs targeting both parts simultaneously. Data on each of these three groups of ADAs will be summarized by arm as described in the following.

A subject is considered positive for ADAs targeting one part (PD-L1 or 4-1BB) if:

- Negative at baseline and at least one positive post-baseline result for that part (assay specific), or
- Positive at baseline and at least one positive post-baseline result with a titer higher than baseline for that part (assay specific)

A subject is considered positive for ADAs targeting both parts if the subject is considered ADA positive for each part, as described above, at the same time.

Of note, ADA positivity requires confirmation in 2 assay steps. Only confirmed ADA positivity results will be considered as positive. Titers for ADA positivity confirmation will be listed.

The number and percentage of subjects with ADAs will be summarized overall and by time point. Of note, subjects with no post-baseline ADA assessment will have a missing ADA status. Immunogenicity data will be listed.

Positive/negative host immune response to each part of GEN1046 will be tabulated at baseline and at any post-baseline visit for each target. Associations between ADA status (positive/negative) and PK concentrations (GEN1046), major safety signals and efficacy information may be explored.

6.8 Interim Analysis

Interim analysis for futility will be performed separately for each cohort (including subcohorts) after at least 10 subjects of a given cohort have been treated and had at least 1 response assessment post-baseline. The docetaxel combination cohort will follow the 6 + 6 design and be evaluated accordingly (see Protocol Section 4.1.2.1 for more details).

A Bayesian predictive probability approach will be used to determine the futility criteria (Lee and Liu, 2008). At the time of each interim analysis, the PPoS will be calculated, which is the probability of achieving success should the cohort be continued to the maximum sample size of 40, given the data observed at interim, and a cohort is considered "success" if the predictive probability that the ORR exceeds the response rate of current standard of care (p_0) is greater than 70%.

The PPoS can be calculated for any cohort size and at any interim time. If the PPoS is low, the data indicate that the treatment may not be efficacious. If the PPoS is <20% (ie, 0 or 1 responders among the first 10 subjects) (see Table 12), the data indicate that it is unlikely the ORR will be better than the response rate of current standard of care at the end of the cohort, given interim results, and the cohort could be stopped early due to insufficient activity. On the other hand, if the PPoS is >70%, the data suggest that if the same trend continues, there is a high probability to conclude a "success" at the end of the cohort. The PFS and OS will also be evaluated at the time of the interim analysis. A cohort may be stopped early by the sponsor if PPoS is low.

Both the confirmed and unconfirmed CR or PR observed at interim will be counted as a response for the calculation of PPoS. Weak priors are chosen for the distribution of response rate: Beta (1.10, 1.90) when p_0=10% and Beta (1.15, 1.85) when p_0=15%. With these distributions, the modes of the response rates are 10% and 15%, respectively.

Table 12. PPoS Based on Responses in the First 10 Subjects

Cancer type	**NSCLC (2L only), Urothelial, TNBC, and Cervical**	**NSCLC (1L, including anti PD-1 Combo), Endometrial, and SCCHN**
ORR that warrants further evaluation of the drug	p_1=25%	p_1=30%
Ineffective drug threshold (ORR ≤ p_0)	p_0=10%	p_0=15%
No of responders in the first 10 subjects	**PPoS**	
0	<1%	0.5%
1	25%	14%
2	66%	47%
3	92%	80%
4	99%	96%
≥5-10	100%	100%

p_0 reflects the response rate of the current standard of care.

1L=first-line; 2L=second-line; NSCLC=non-small cell lung cancer; ORR=objective response rate; p_1=ORR that warrants further evaluation of the drug; PPoS=predicted probability of success; SCCHN=squamous cell carcinoma of the head and neck; TNBC=triple-negative breast cancer.

The operating characteristics of the design based on 40,000 simulation runs are summarized in Table 13. If the true ORR is less than 10%, there is reasonable chance to reach the futility criteria at interim. On the other hand, if the true ORR is 35% or higher, the probability to stop for futility is very low (<9%).

After 10 subjects, the PPoS can be calculated continuously (ie, after each 5 new subjects in a cohort) to monitor the treatment efficacy. The predictive probabilities/PPoS were calculated using the R package phbye v0.1.4 in R v3.4.4.

In addition to the interim analysis for futility, interim data from the trial may be presented at scientific meetings such as eg, the annual meetings of the American Society of Clinical Oncology and/or the European Society for Medical Oncology.

Interim Futility Analysis of Expansion Cohort EC1

An interim futility analysis will be conducted for EC1 at ~12 weeks (ie, after second post-baseline tumor assessment) after the 40th subject is treated. If no greater than 6 subjects have objective responses (including unconfirmed response), the sponsor may discontinue the enrollment of additional subjects in EC1.

Table 13. Operating Characteristics of the Predictive Probability Design

			Interim Analysis 1 (n=10)		**Interim Analysis 2 (n=20)**	
p0	p1	True ORR	Futility Limit (# of responders)	Pr(Futility)	Futility Limit (# of responders)	Pr(Futility)
10%	25%	10%	0	35%	1	39%
		15%	0	20%	1	18%
		20%	0	11%	1	7%
		25%	0	6%	1	2%
		30%	0	3%	1	0%
		35%	0	1.4%	1	0%
15%	30%	10%	1	74%	2	68%
		15%	1	54%	2	41%
		20%	1	38%	2	20%
		25%	1	25%	2	9%
		30%	1	15%	2	4%
		35%	1	9%	2	1%

p0 reflects the response rate of the current standard of care.

n=number of subjects; ORR=objective response rate; p1=ORR that warrants further evaluation of the drug; Pr(Futility)=probability of futility.

Table 14. 95% Confidence Interval of ORR Estimates

Sample Size/ORR observed	**20%**	**25%**	**30%**	**35%**
20	6%, 44%	9%, 49%	12%, 54%	15%, 59%
40	9%, 36%	13%, 41%	17%, 47%	21%, 52%
140	14%, 28%	18%, 33%	23%, 38%	27%, 44%

ORR=objective response rate.

6.9 Data Monitoring Committee

The study conduct and safety of participants will be monitored by an independent DMC. The roles, responsibilities and regulations governing the Committee are detailed in a separate charter. The DMC will convene every 3 months in each study phase. Analysis specifications for those meetings are provided in a separate document (DMC TLFs Shells).

6.10 Changes to Methods Planned in the Protocol

Table 3-2 in the protocol (v10.0) indicates that for EC1, the primary endpoint (ORR) and secondary endpoints (DoR and PFS) will be assessed by an Independent Review Committee (IRC). See bold type below. The IRC assessment will be removed in the next protocol amendment (protocol amendment 9.0). This is reflected in SAP Section 2.0.

Objectives and Endpoints – Expansion Cohort EC1

Objectives	Endpoints
Primary	
• Evaluate clinical efficacy	• Objective Response Rate (ORR) per RECIST 1.1 **assessed by Independent Review Committee (IRC)**
Secondary	
• Evaluate the safety profile of GEN1046	• Adverse events (AEs) and safety laboratory parameters
• Further evaluate clinical efficacy	• Duration of response (DoR), PFS per RECIST 1.1 **assessed by IRC**
	• ORR, DoR, PFS per RECIST 1.1 assessed by investigator
	• Overall survival (OS)
• Characterize PK and immunogenicity of GEN1046	• PK parameters
	• Anti-Drug Antibody (ADA) response
Exploratory	
• To assess pharmacodynamics and potential biomarkers of GEN1046	• Immune system activation (eg, immune subset shift, tumor immune cell infiltration etc)
• To assess anti-tumor activity based on iRECIST	• Anti-tumor activity, ie, reduction in tumor size according to iRECIST
	• iORR

EC=expansion cohort; iORR=immune objective response rate; iRECIST=immune Response Evaluation Criteria in Solid Tumors; PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors.

7. Tables, Listings and Figures

7.1 Programming Guidelines

Computer-generated output will adhere to the following specifications. The standard operating procedures (SOPs) of Syneos Health Clinical will be followed in the creation and quality control of all tables, listings and figures.

7.1.1 Format of Output

Unless otherwise specified, all computer-generated output should be produced in landscape mode. Required margins: at least 1.25 inches on top (the binding margin [or left for portrait output]), at least 1 inch on right, left, and bottom. Courier new font size 8 will be used (the smallest acceptable point size to the Regulatory Authorities). All output should have the Sponsor name, protocol number, the type of delivery, and page number. Tables/listings/figures should be internally paginated in relation to total length (i.e., page number should appear sequentially as page n of N, where N is the total number of pages in the table).

All output should have the following header at the top of the page:

```
Genmab Protocol GTC1046-01 (PPD                    )    Confidential          Page x of y
Draft/Final Run: ddMMMyyyy
```

All output should have the following footer at the bottom of the page:

```
Program Name: xxx.SAS
```

1. Output numeration will conform to International Conference on Harmonization (ICH) recommendations. The study population should be identified immediately following the title.
2. Column headings should be in initial upper-case characters.
3. For numeric variables, include “unit” in column or row headings where appropriate.
4. Footnotes should be single spaced. The notes are aligned vertically by the left vertical border of the table.
5. If the categories are not ordered (e.g., race), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
6. An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
7. Listings should be sorted by phase, dose levels (escalation) or cohort (expansion), subject numbers and assessment date.
8. In a listing, display the subject number only once for the subject with multiple records. If a subject’s records run into multiple pages, display the subject number once for every page.
9. For tables and figures, the last footnote will be ‘Table/Figure Generation: ddmmmyyyy hh:mm Listing Source: 16.2.x.’; and for listings ‘Listing Generation: ddmmmyyyy hh:mm’

7.1.2 Format of Data

1. Unless otherwise specified for continuous variables, the estimated mean, standard deviation and median for a set of values should be printed out to 1 more significant digit than the individual units of measurement. The minimum and maximum should report the same significant digits as the original values.
2. Data in columns of a table should be formatted as follows:
   - Alphanumeric values are left-justified.
   - Whole numbers (e.g., counts) are right-justified.
   - Numbers containing fractional portions are decimal aligned.
3. Unless otherwise specified, percentage values should be printed with 1 digit to the right of the decimal point (e.g., 12.8%, 5.4%). Less-than signs "<0.1%" should be printed when values are >0.0 and <0.1% (not 0.0%).
4. Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote (" - = unknown or not evaluated"), or as "N/A," with the footnote "N/A = not applicable," whichever is appropriate.
5. Dates should be printed in SAS DATE9.format ("DDMMMYYYY": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
6. Time should be printed in SAS TIME5.format ("HH:MM": 17:30). Missing portions of time should be represented on subject listings as dashes (--:30). Times that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

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9. Appendices

See the TLF shells appended to this SAP.

9.1 Appendix 1.

Classification of Confirmed Best Overall Response

Overall response at initial time point	**Overall response at subsequent time point**	**Best overall response (BOR) with response confirmation per RECIST 1.1**
CR	CR at least 4 weeks after initial CR For example: 1) CR, CR with the second CR at least 4 weeks after the initial CR, or 2) multiple consecutive CRs (for example CR, CR, CR) with the last CR at least 4 weeks after initial CR {Below (PR, PR), (PR, CR) scenarios follow same approach}	CR
CR	PR	Query site - this should never happen.
CR	CR less than 4 weeks after initial CR	SD
CR	SD	Query site - this should never happen.
CR	PD	SD if the CR is at least 5 weeks from first dose, otherwise PD
CR	Not Evaluable (NE) or no subsequent assessment	SD if the CR is at least 5 weeks from first dose, otherwise NE
CR	one scheduled NE prior to CR (at least 4 weeks between two CRs)	CR
PR	CR at least 4 weeks after initial PR	PR
PR	PR at least 4 weeks after initial PR	PR
PR	CR less than 4 weeks after initial PR	SD
PR	PR less than 4 weeks after initial PR	SD
PR	SD	SD
PR	PD	SD if the PR is at least 5 weeks from first dose, otherwise PD
PR	NE or no subsequent assessment	SD if the PR is at least 5 weeks from first dose, otherwise NE
PR	<=2 NE prior to PR OR one SD prior to PR (at least 4 weeks between two PRs)	PR
PR	More than 1 SD, followed by PR or CR	SD
SD	NE, SD or no subsequent assessment	SD if there is SD at least 5 weeks from first dose, otherwise NE
SD	PD	SD if the SD is at least 5 weeks from first dose, otherwise PD
PD	any assessment or no assessment	PD

Treat Non-CR/Non-PD equivalent to SD.

The BOR is the most favorable visit response recorded since the start of therapy, and prior to any visit response of PD
A best response of PR or CR requires confirmation, as follows:
- A PR has to be followed at least 4 weeks later by another PR or CR
o <=2 Intervening NE visits do not prevent confirmation of the PR
- A CR has to be followed at least 4 weeks later by another CR
o For CRs, only one intervening scheduled visit can be NE; multiple scheduled intervening NE visits mean that another confirmation is required
o Intervening unscheduled scans with a response of NE do not prevent confirmation

For a best response of SD, no confirmation is required, but if SD is being considered as the best response, a visit with a response of SD or better must be seen at least 5 weeks after first dose for SD to be assigned as the best response.

In ADaM ADRS, for subjects with a response of 'NA', eligibility for analysis will be determined as follows:

For unconfirmed response, patients are considered eligible if it is more than four weeks between first dose and data-cut date and if the patient has either stopped treatment or did have a measurement after at least 4 weeks after treatment start date.

For confirmed response, patients are considered eligible if it is more than four weeks between first dose and data-cut date and if the patient has either stopped treatment and has a maximum of one post-baseline scan or did have at least two valid post-baseline measurements.

If the subject is ongoing in the study (end of study date, EOSDT = .) and the duration between the data cutoff date and treatment start date is within 7 weeks (49 days) then they are truly the 'NA' subjects; else set to 'NE'.

ELIGFL: if BOR ne 'NA' then ELIGFL = 'Y'

This definition applies for both best confirmed AND unconfirmed responses.

9.2 Appendix 2.

Classification of PTs in Specific Groups.

The group terms are as follows:

Anemia

Lymphocyte count decreased

Neutropenias

Thrombocytopenia

Colitis and immune mediated enterocolitis

Pancreatitis, Immune mediated pancreatitis

Hyperglycemia, Type 1 diabetes mellitus

Infusion-related reactions

CCI [redacted]

Immune-mediated Adverse Events

Asthenic Condition

Abdominal Pain

The precise list of PTs will be included in the ADaM specifications as a complex algorithm.

Genmab-GCT1046-01_SAP Text_v2.0

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