CLINICAL TRIAL PROTOCOL

First-in-human, Open-label, Dose-escalation Trial With Expansion Cohorts to Evaluate Safety of GEN1046 in Subjects With Malignant Solid Tumors

Short Title: GEN1046 Safety Trial in Patients With Malignant Solid Tumors

Protocol Number:	GCT1046-01
Sponsor Name:	Genmab*
Clinical Research Organization:	Syneos Health™ 3201 Beechleaf Court, Suite 600 Raleigh, NC 27604, USA
Regulatory Agency Identifier Number(s):	IND: 141147 EU CT: 2023-509059-15-00 NCT03917381
Investigational Medicinal Product (IMP):	GEN1046 (DuoBody®-PD-L1×4-1BB)
Development Phase:	1/2a
Protocol Approver**	**Name** PPD, MD **Title** PPD
Date of Protocol (Version):	20-Sep-2024 (Protocol Amendment 11, v13.0) 30-Jan-2024 (Protocol Amendment 10, v12.0) 13-Dec-2023 (Protocol Amendment 9, v11.0) 06-Oct-2022 (Protocol Amendment 8, v10.0) 27-Jun-2022 (Protocol Amendment 7, v9.0) 21-Feb-2022 (Protocol Amendment 6, v8.0) 06-Oct-2021 (Protocol Amendment 5, v7.0) 27-Jul-2021 (Protocol Amendment 4, v6.0) 28-Apr-2021 (Protocol Amendment 3, v.5.0) 14-Apr-2021 (Protocol Amendment 2, v.4.0) 19-Nov-2019 (Protocol Amendment 1, v.3.0) 02-Nov-2018 (Original Protocol, v.2.0) 02-Nov-2018 (Protocol not submitted, v.1.0)

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** This protocol was approved via electronic signature on the approval page appended to the document.

SPONSOR INFORMATION PAGE

Sponsor information for all countries in the European Union, Georgia, and Israel	Genmab A/S Carl Jacobsens Vej 30 2500 Valby Denmark
Sponsor information for all other countries	Genmab US, Inc. 777 Scudders Mill Rd Plainsboro, New Jersey 08536 United States of America

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STATEMENT OF COMPLIANCE

Good Clinical Practice (GCP) Compliance

This trial will be conducted in compliance with the principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice (ICH GCP E6[R2]), and applicable regulatory requirements.

Confidentiality Statement

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ABBREVIATIONS AND DEFINITION OF TERMS

1L	first-line (frontline)
1Q1W	once (1 dose) every week
1Q3W	once (1 dose) every 3 weeks
1Q3Wx2	Days 1 and 22
1Q6W	once (1 dose) every 6 weeks
2L	second-line
5-FU	5-fluorouracil
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
beta-hCG	beta-human chorionic gonadotropin
BLRM	Bayesian logistic regression model
BOR	best overall response
BRCA	breast cancer gene
C1D1	Cycle 1 Day 1
cfDNA	cell-free DNA
C_{max}	maximum concentration
CNS	central nervous system
CPI	checkpoint inhibitor
CR	complete response
CrCl	creatinine clearance
CRM	continual reassessment method
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor-derived DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTR	Clinical Trial Registration
CYP	cytochrome P450

DCR	disease control rate
DEC	Dose Escalation Committee
DL	dose level
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
dMMR	deficient mismatch repair
DoR	duration of response
EC	expansion cohort
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
ER	estrogen receptor
EU	European Union
EWOC	Escalation with Overdose Control
FAS	full analysis set
Fc	fragment crystallizable
FcγR	Fc γ receptor
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FIH	first-in-human
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GM-CSF	granulocyte/macrophage colony stimulating factor
HER	human epidermal growth factor receptor
HLH	hemophagocytic lymphohistiocytosis
HPV	human papillomavirus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
iCR	iRECIST complete response
IEC	Independent Ethics Committee
IFN	Interferon
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin

IMP	investigational medicinal product
iORR	immune objective response rate
iPR	iRECIST partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
IV	intravenous(ly)
LLOQ	lower limit of quantification
mAb	monoclonal antibody
MABEL	minimally-anticipated biological effect level
mCRM	modified Continuous Reassessment Method
MoA	mechanism of action
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NOAEL	no-observed-adverse-effect-level
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic(s)
PPoS	predictive probability of success
PR	partial response
PT	prothrombin time
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RO	receptor occupancy
ROS1	c-ROS oncogene 1
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan

SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	Safety Committee
SCCHN	squamous cell carcinoma of the head and neck
sCD25	soluble interleukin-2 receptor
SD	stable disease
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TC	tumor cells for CCI Assay scoring algorithm
TCR	T-cell receptor
TEAE	Treatment emergent adverse event
TIL	tumor-infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
TMB	tumor mutational burden
TME	tumor microenvironment
TNBC	triple-negative breast cancer
TNF	tumor necrosis factor
TPS	tumor proportion score
TRAE	treatment-related adverse event
UC	urothelial carcinoma
ULN	upper limit of normal
US	United States
USA	United States of America

Definition	
Trial drug	GEN1046
Trial treatment	Trial treatment is any individual component or combination of components in the treatment regimen, per respective cohort as described in Table 1-1.

PROTOCOL AMENDMENTS

Protocol/Amendment No; Version	Issue Date
Original Protocol; Version 1.0 (protocol not submitted) (TMF-03393)	02-Nov-2018
Original Protocol; Version 2.0 (TMF-03393)	02-Nov-2018
Global Amendment 1; Version 3.0 (TMF-03393)	19-Nov-2019
Global Amendment 2; Version 4.0 (TMF-03393)	14-Apr-2021
Global Amendment 3; Version 5.0 (TMF-03393)	28-Apr-2021
Global Amendment 4; Version 6.0 (TMF-03393)	27-Jul-2021
Global Amendment 5; Version 7.0 (TMF-03393)	06-Oct-2021
Global Amendment 6; Version 8.0 (TMF-03393)	21-Feb-2022
Global Amendment 7; Version 9.0 (TMF-03393)	27-Jun-2022
Global Amendment 8; Version 10.0 (TMF-03393)	06-Oct-2022
Global Amendment 9; Version 11.0 (TMF-03393)	13-Dec-2023
Global Amendment 10; Version 12.0 (TMF-03393)	30-Jan-2024
Global Amendment 11; Version 13.0 (TMF-03393)	20-Sep-2024

Amendment 11 (20-Sep-2024)

This amendment is considered a substantial modification based on the criteria set forth in Article 2(13) of the EU Clinical Trial Regulation and the Council of the European Union.

Overall Rationale for Global Amendment 11:

The timing of the primary analyses was defined in this protocol amendment. Once the trial has reached the primary analysis cutoff date, non-essential PK/ADA/biomarker(s) assessments will no longer be collected, and laboratory tests will only be done locally. As such, a new post-primary analysis schedule of activities is included. In addition, this amendment includes language to ensure compliance with European Union (EU) Clinical Trial Registration (CTR) 536/2014, and clarifications and consistencies.

The amendment changes are summarized below. Changes included in the summary of changes table are incorporated in the trial synopsis. Section and table numbers are as per Amendment 11.

List of Changes in the Protocol and Their Rationales

Section No. and Name	Description of Change	Brief Rationale
• Global	• Removed references to individual schedule of activities (SOA) tables and replaced with reference to Section 1.3. • Changed “trial drug” and “GEN1046” to “trial treatment” to incorporate combination treatment, as applicable.	• Update
• Section 1.2.1 Expansion Cohorts (EC) Table	• Updated subcohorts for EC3 and EC8	• Clarification

Section No. and Name	Description of Change	Brief Rationale
• Section 1.3 Schedule of Activities • Section 1.3.4 Post-Primary Analysis Schedule of Activities – All Subjects • Section 4.1 Description of Trial Design, Section 9.2.1 Definition of Target and Non-target Disease, Section 9.4.3 Electrocardiograms, Section 9.5 Clinical Laboratory Assessments, Section 12.3 Data Quality Management	• Note added to all schedule of activities (SOA) tables to reference the new table (Table 1-23: Post-Primary Analysis Schedule of Activities-All Subjects). • New Table 1-23 with reduced assessments was added. • Removed requirement for images/assessments to be submitted to central imaging vendor or central laboratory	• To remove collection of non-essential assessments and central laboratory testing once the trial reaches the primary analysis cutoff date as detailed in the overall rationale above.
• Section 1.2.1 Expansion Cohorts Table 1-1 • Section 4.4.1.3 Expansion Cohorts EC11A and EC11B (GEN1046-Pembrolizumab Combinations)	• Added language regarding pembrolizumab treatment duration for EC11	• Clarification on the use of pembrolizumab.
• Section 1.3 Schedule of Activities: Table 1-2	• Corrected the window for on-trial imaging at Week 6 from –7 days to ±7 days.	• Correction
• Section 1.3 Schedule of Activities: Table 1-2, Table 1-6, Table 1-7, Table 1-8, Table 1-9, Table 1-10, and Table 1-11	• Footnote added to clarify timing of safety follow-up visit prior to starting new anti-cancer treatment. • Footnote amended to indicate that only SAEs related to trial treatment should be reported during post-treatment period.	• Clarification. • Correction.
• Section 1.3 Schedule of Activities: Table 1-2, Table 1-6, Table 1-7, Table 1-8, Table 1-9	• For the unscheduled visit, replaced footnote 12 with footnote 11.	• Correction
• Section 1.3 Schedule of Activities: Table 1-7	• Corrected the visit window from -7 days to ±3 days for the Cycle 4-Cycle X (1Q6W) Day 22 column.	• Correction
• Section 1.3 Schedule of Activities: Table 1-7, Table 1-8, Table 1-9, Table 1-10, Table 1-11	• Amended footnote to reflect that the visit window (±3d) does not apply to C1D1.	• Clarification
• Section 1.3 Schedule of Activities: Table 1-9	• ECOG test was added at Cycle 5 and onwards for D1 and D22.	• Correction
• Section 1.3 Schedule of Activities: Table 1-10 and Table 1-11	• Hepatitis C assessment was removed. • Footnote clarified to add study days for collection of central labs for hematology and biochemistry assessments.	• Per exclusion criterion 11, patients with known medical history or ongoing hepatitis C infection that has not been cured were ineligible for this study.

Section No. and Name	Description of Change	Brief Rationale
	• Added hepatitis B assessment at the treatment discontinuation visit to align with associated footnote. • Moved footnote 19 from X under CCI CCI Cycles 7-X to Cycles 5-6.	• Clarification • Correction • Correction
• Section 1.3 Schedule of Activities: Table 1-22	• Updated table to align with footnote (first on-treatment biopsy should be taken between C2D8-C2D15 and not on C1D8).	• Correction
• Section 2.3 Benefit-Risk Assessment	• Removed trial-specific data and added a reference to the Investigator's Brochure (IB).	• The IB contains the latest clinical trial information.
• Section 3 Objectives and Endpoints, Table 3-1 and Table 3-2	• Clarified that determination of MTD and/or RP2D was for the dose escalation cohorts only (Table 3-1). • Removed assessment by IRC requirement for primary and secondary endpoints of ORR, DoR, and PFS (Table 3-2).	• Clarification • Investigator assessment was considered sufficient due to the small sample size of these cohorts and the exploratory nature of the trial.
• Section 4.5.1 Estimated Trial Duration for an Individual Subject	• New section added	• EU CTR compliance
• Section 4.5.2. End of Trial	• End of trial definition and maximal trial duration were updated. Post-trial treatment language removed due to repetition with Section 4.5.5.	• Clarification
• Section 4.5.5 Trial Termination	• Added reference to end of trial section and removed repetitive language.	• Clarification
• Section 6.2. Dosage and Administration • Appendix 4 Country Specifics, Table 17-3	• Added a reference to new Table 17-3 for IMP authorization status. • Updated language to reflect that all study treatment in this trial is considered IMP.	• EU CTR compliance • To comply with the CTAG guidance document update from March 2024 "Recommendations on the use of Auxiliary Medicinal Products in Clinical Trials"
• Section 6.4.2.1 Premedication and Antiemetics for Subjects Receiving Combination Therapy	• Added recommendation for corticosteroids with pemetrexed treatment.	• To prevent skin toxicity.
• Section 6.7 Docetaxel, Pembrolizumab, Cisplatin/Carboplatin, Pemetrexed, Paclitaxel, and Nab-paclitaxel	• Removed section	• Text was repetitive with Section 6.5.
• Section 7.3.1.1 Immune-Related Adverse Events (irAEs), Table 7-1	• Removed reference to CTCAE v5.0 from toxicity grade • Added footnote for hypothyroidism dose modification • Added management for myocarditis	• Grading of events is based on CTCAE and ASCO guidelines. • Consistency with updated pembrolizumab guidance

Section No. and Name	Description of Change	Brief Rationale
	• Add G4 toxicity management for skin toxicities.	
• Section 7.3.1.3.1 Cytokine Release Syndrome	• Added clarification for continuation of trial treatment for subjects with CRS.	• Clarification
• Section 7.3.1.3.2 Hemophagocytic Lymphohistiocytosis	• Section updated to reflect latest guidance.	• Update
• Section 7.3.6 Pemetrexed, Table 7-12	• Corrected/added the platelet and ANC units.	• Correction
• Section 8.1 Discontinuation of Treatment	• Removed redundant language	• Clarification
• Section 8.4 Safety Follow-Up Evaluations	• Corrected language to reflect that subjects will move into survival follow-up after safety follow-up visits.	• Correction
• Section 10.8 Annual Safety Reporting by the Sponsor	• Added new section.	• EU CTR compliance
• Section 11.6.4 Safety Sensitivity Analysis • Section 11.10.6 Efficacy Sensitivity Analysis	• Added new sensitivity analyses.	• To assess impact of a potential long period where subjects could be exposed to only trial medications other than GEN1046
• Section 11.12.2 Primary Analysis • Section 11.12.3 Final Analysis	• Added new sections.	• To define the time period for the primary and final analysis.
• Section 13.1.1 Trial and Site Start and Closure	• Post-trial treatment language removed due to repetition with Section 4.5.5.	• Clarification
• Section 13.2.1 Regulatory and Ethical Considerations • Section 13.2.5 Data Protection • Section 13.2.6 Dissemination of Clinical Trial Data • Section 15 Lay Protocol Synopsis	• Added new section. • Added new language regarding potential data breach. • Added/updated new language regarding public registration of protocol information. Removed previous Section 14.7 (Registration of Clinical Trials and Disclosure of Results). • Added new section.	• EU CTR compliance
• Appendix 4 Country Specifics, Table 17-2	• Table 17-2 (Expansion Cohorts) was updated to reflect that cohorts EC11, 12, and 13 include global sites and that enrollment was completed for all cohorts	• Update
• Throughout the protocol	• Administrative changes and minor updates were made.	• Administrative changes and for clarification of text.

1 PROTOCOL SUMMARY

1.1 Trial Synopsis

Title	First-in-human, Open-label, Dose-escalation Trial With Expansion Cohorts to Evaluate Safety of GEN1046 in Subjects With Malignant Solid Tumors
Brief Title	GEN1046 Safety Trial in Patients With Malignant Solid Tumors
Clinical Phase	Phase *1/2a*
Purpose and Rationale	GEN1046 is a PD-L1×4-1BB bispecific antibody that induces conditional activation of T cells through 4-1BB stimulation, which is dependent on simultaneous binding to programmed death-ligand 1 (PD-L1). The fragment crystallizable (Fc) domain of GEN1046 was engineered to silence interactions with the Fc γ receptor and the complement factor C1q. Thereby, GEN1046-mediated stimulation of 4-1BB signaling in activated T cells is strictly dependent on simultaneous binding of the PD-L1-binding arm. In addition, the PD-L1-specific arm of GEN1046 functions as a classical immune checkpoint inhibitor by blocking the programmed cell death protein 1 (PD-1)/PD-L1 axis, also in the absence of 4-1BB binding. The hypothesis is that by simultaneous binding of PD-L1 on tumor cells or antigen presenting cells and 4-1BB on tumor-specific T cells, GEN1046 will induce efficacious T-cell activation in the tumor or in tumor-draining lymph nodes, thereby enhancing anti-tumor immunity.

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) (dose escalation only)	• Dose-limiting toxicity (DLT)
• Establish safety profile of GEN1046	• Adverse events (AEs) and safety laboratory parameters
Secondary	
• Evaluate the safety profile of GEN1046 in combination with docetaxel (EC9 only)	• AEs and safety laboratory parameters
• 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 pharmacokinetics (PK) profile of GEN1046	• PK parameters
• Evaluate immunogenicity of GEN1046	• Anti-Drug Antibody (ADA) response

<table>
<tr><td></td><td><table>
<tr><td>• Evaluate anti-tumor activity</td><td>• Anti-tumor activity, ie, reduction in tumor size according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1:
• Objective Response Rate (ORR)
• Disease Control Rate (DCR)
• Duration of Response (DoR)</td></tr>
<tr><td>Exploratory</td><td></td></tr>
<tr><td>• To assess pharmacodynamics and potential biomarkers of GEN1046
• To assess anti-tumor activity based on immune Response Evaluation Criteria in Solid Tumors (iRECIST)
• Evaluate efficacy</td><td>• Immune system activation (eg, immune subset shift, tumor immune cell infiltration, etc)
• Anti-tumor activity, ie, reduction in tumor size according to iRECIST
  • immune ORR (iORR)
• Progression-free survival (PFS)
• Overall survival (OS)</td></tr>
</table></td></tr>
<tr><td>Objectives and Endpoints – Expansion Cohort EC1</td><td><table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary</td><td></td></tr>
<tr><td>• Evaluate clinical efficacy</td><td>• ORR per RECIST 1.1</td></tr>
<tr><td>Secondary</td><td></td></tr>
<tr><td>• Evaluate the safety profile of GEN1046</td><td>• AEs and safety laboratory parameters</td></tr>
<tr><td>• Further evaluate clinical efficacy</td><td>• DoR, PFS per RECIST 1.1
• OS</td></tr>
<tr><td>• Characterize PK and immunogenicity of GEN1046</td><td>• PK parameters
• ADA response</td></tr>
<tr><td>Exploratory</td><td></td></tr>
<tr><td>• To assess pharmacodynamics and potential biomarkers of GEN1046</td><td>• Immune system activation (eg, immune subset shift, tumor immune cell infiltration, etc)</td></tr>
<tr><td>• To assess anti-tumor activity based on iRECIST</td><td>• Anti-tumor activity, ie, reduction in tumor size according to iRECIST
• iORR</td></tr>
</table></td></tr>
<tr><td>Trial Design</td><td>This is an open-label, multicenter, 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). 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.</td></tr>
<tr><td>Population</td><td>Approximately 725 subjects can be enrolled in the trial.

The dose escalation part planned to enroll approximately 100 subjects with metastatic or unresectable solid tumors for whom there is no available standard therapy likely to confer clinical benefit, or subjects who are not candidates for such available therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN1046 may be beneficial. In total, 61 subjects had been enrolled in the dose escalation part when enrollment was completed.</td></tr>
</table>

	The expansion is planned to enroll approximately 652 subjects with relapsed or refractory, advanced and/or metastatic non-small cell lung cancer (NSCLC), first-line (1L) NSCLC (non-squamous and squamous), endometrial carcinoma, urothelial carcinoma (UC), triple-negative breast cancer (TNBC), squamous cell carcinoma of the head and neck (SCCHN), or cervical cancer who are no longer candidates for standard therapy (if subjects had access and were eligible for the respective treatments), and for whom, in the opinion of the investigator, experimental therapy with GEN1046 alone and in combination may be beneficial.
Key Inclusion Criteria	**For Dose Escalation:** • Subjects must have a histologically or cytologically confirmed non-central nervous system (CNS) solid tumor that is metastatic or unresectable and for whom there is no available standard therapy likely to confer clinical benefit, or subjects who are not candidates for such available therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN1046 may be beneficial. **For Expansion:** ***Expansion Cohort 1 (NSCLC): PD-1/L1 Pretreated (100 mg once every 3 weeks [1Q3W])*** • Subjects with NSCLC who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of 1 treatment line) for metastatic disease with radiographic disease progression on or after last prior treatment. • Subjects with NSCLC of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an epidermal growth factor receptor (EGFR)-sensitizing mutation and/or anaplastic lymphoma kinase (ALK) translocation/c-ROS oncogene 1 (ROS1) rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved tyrosine kinase inhibitor (TKI). Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment. • Subjects should have received platinum-based therapy (or alternative chemotherapy due to platinum ineligibility, eg, a gemcitabine-containing regimen). • Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor approval is required for subjects with a best overall response (BOR) of stable disease (SD) or progressive disease (PD) on a checkpoint inhibitor (CPI) containing regimen with a treatment duration of up to 16 weeks. • Local results from the most recent PD-L1 test must be provided prior to enrollment. If local PD-L1 test results are unavailable, sponsor approval for enrollment is required. ***Expansion Cohort 2 (NSCLC) – PD-1/L1 Naive*** • Subjects with NSCLC of any histology may be enrolled. Subjects with NSCLC who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of 1 treatment line) for metastatic disease with radiographic disease progression on or after last prior treatment. • Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.

	• Subjects should have received platinum-based therapy (or alternative chemotherapy due to platinum ineligibility, eg, a gemcitabine-containing regimen). • Subjects must not have received prior treatment with a PD-1/L1 inhibitor. ***Expansion Cohort 3 (UC):*** • Subjects with UC (of the bladder, ureter, urethra, or renal pelvis) with predominantly transitional-cell features on histology who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of 1 treatment line) for locally advanced/metastatic disease with radiographic disease progression on or after last prior treatment. • Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor approval is required for subjects with a BOR of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks. • Local results from the most recent PD-L1 test should be provided prior to enrollment (if available). ***Cohort 3a: For Subjects who are Eligible to Receive Platinum-Based Therapy:*** • Subjects must have received platinum-based chemotherapy. ***Cohort 3b: For Subjects Ineligible to Receive Platinum-Based Therapy:*** • Subjects must not be eligible for any platinum-based or any cisplatin-containing chemotherapy. ***Expansion Cohort 4 (Endometrial Cancer):*** • Subjects with endometrial cancer who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of 1 treatment line) for advanced/metastatic disease with radiographic disease progression on or after last prior treatment. • Subjects must have epithelial endometrial histology including: endometrioid, serous, squamous, clear-cell carcinoma, or carcinosarcoma. *Note*: Sarcomas and mesenchymal endometrial cancer are excluded. • Subjects must not have received prior treatment with a PD-1/L1 inhibitor (established local label/access need to be respected). • Local results of the most recent deficient mismatch repair (dMMR) or microsatellite instability (MSI) status as per local assessment should be provided prior to enrollment (if available). ***Expansion Cohort 5 (TNBC):*** • TNBC defined as human epidermal growth factor receptor 2 (HER2)-negative (HER2 is negative by fluorescence in situ hybridization) assay (non-amplified ratio of HER2 to CEP17 <2.0 single probe average HER2 gene copy number <4 signals/cell) or alternatively HER2 protein expression by immunohistochemistry (IHC) result is 1+ negative or IHC 0 – negative and estrogen receptor and progesterone receptor negative status (defined as <1% of cells expressing hormonal receptors via IHC analysis) as per local assessment. Subjects who have received up to 4 prior systemic treatment regimens including but not limited to anthracycline-, taxane-, antimetabolite-, or microtubule inhibitor-containing regimens (maintenance treatment is considered being part of 1 treatment line) for locally advanced/metastatic disease with radiographic disease progression on or after last prior treatment. Local pathological confirmation of triple-negative disease is required prior to trial entry.

	• Subjects with a prior history of a breast cancer with a different phenotype must have confirmation of TNBC from a biopsy obtained after the subject's last prior systemic therapy. • Local results of the most recent dMMR or MSI status as per local assessment should be provided prior to enrollment (if available). ***Cohort 5a – Subjects Who Have Received Prior Treatment with a PD-1/L1 Inhibitor:*** • Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor approval is required for subjects with a BOR of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks. • Local results from the most recent PD-L1 test should be provided prior to enrollment (if available). ***Cohort 5b – Subjects Who Have Not Received Prior Treatment with a PD-1/L1 Inhibitor:*** • Subjects must <u>not</u> have received prior treatment with a PD-1/L1 inhibitor (established local label/access need to be respected). ***Expansion Cohort 6 (SCCHN):*** • Subjects with recurrent or metastatic SCCHN (oral cavity, pharynx, larynx) who have received up to 4 prior systemic treatment regimens for recurrent/metastatic disease with radiographic PD on or after last prior treatment (maintenance treatment is considered being part of 1 treatment line). • Subjects must have disease progression on or after prior therapy with platinum-based chemotherapy (alternative combination chemotherapy is acceptable if the subject's platinum ineligibility status is documented). ***Cohort 6a – Subjects Who Have Received Prior Treatment with a PD-1/L1 Inhibitor:*** • Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor approval is required for subjects with a BOR of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks. • Local results from the most recent PD-L1 test should be provided prior to enrollment (if available). ***Cohort 6b – Subjects Who Have Not Received Prior Treatment with a PD-1/L1 Inhibitor:*** • Subjects must <u>not</u> have received prior treatment with a PD-1/L1 inhibitor (established local label/access need to be respected). ***Expansion Cohort 7 (Cervical Cancer):*** • Subjects with cervical cancer who have received up to 4 prior systemic treatment regimens including chemotherapy in combination with bevacizumab (according to the applicable labeling) unless the subject is ineligible for bevacizumab according to local standards (chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy should not be counted as a prior line of therapy) for recurrent/metastatic disease with radiographic disease progression on or after last prior treatment. • Subjects must have cervical cancer of squamous cell, adenocarcinoma, or adenosquamous histology. • Subjects must <u>not</u> have received prior treatment with a PD-1/L1 inhibitor (established local label/access need to be respected). ***Expansion Cohort 9 (Docetaxel Combination [NSCLC]: GEN1046 in Combination with Docetaxel):*** • Subjects with NSCLC of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must

	not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.
	• Note: Disease progression during/after anti-PD-1/L1 treatment is defined by meeting the following criteria:
	  • Has received at least 2 doses of an approved anti-PD-1/L1 monoclonal antibody (mAb).
	  • Has demonstrated disease progression (PD) during/after PD-1/L1 as defined by RECIST 1.1.
	• Subjects have progressed during/after platinum doublet chemotherapy with or without an anti-PD-1/L1 mAb.
	• No prior treatment with docetaxel. This includes past treatment with monotherapy, combination, and/or any experimental use.
	Expansion Cohort 8 (NSCLC Treatment-Naive for Metastatic Disease: GEN1046 monotherapy):
	• Subjects with metastatic NSCLC who have received no prior systemic treatment regimens for metastatic disease. Subjects must <u>not</u> have received prior treatment with a PD-1/L1 inhibitor. Subjects must have radiographic disease progression on or after last prior treatment. This is not required for subjects who have newly diagnosed disease.
	• Subjects with NSCLC of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.
	• Prior to C1D1, subjects must have a PD-L1 expression result available from a tumor sample from the metastatic stage of the cancer. Tumor PD-L1 expression can be determined by the sponsor-designated central laboratory CCI [redacted] or per site local assessment with CCI PD-L1 CCI [redacted] assay used per manufacturer's instructions.
	• Tumor demonstrates PD-L1 expression in ≥1% of tumor cells (TPS ≥1% or ≥1% TC) as assessed by IHC performed locally or by central laboratory testing.
	Expansion Cohort 11 (NSCLC Treatment-Naive for Metastatic Disease: GEN1046 in Combination with Pembrolizumab):
	• Subjects with metastatic NSCLC who have received no prior systemic treatment regimens for metastatic disease. Subjects must <u>not</u> have received prior treatment with a PD-1/L1 inhibitor. Subjects must have radiographic disease progression on or after last prior treatment. This is not required for subjects who have newly diagnosed disease.
	• Subjects with NSCLC of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.
	• Prior to C1D1, subjects must have a PD-L1 expression result available from a tumor sample from the metastatic stage of the cancer. Tumor

	PD-L1 expression can be determined by the sponsor-designated central laboratory CCI [redacted] or per site local assessment with CCI [redacted] PD-L1 CCI [redacted] assay used per manufacturer's instructions. • Tumor demonstrates PD-L1 expression in ≥1% of tumor cells (TPS ≥1% or ≥1% TC) as assessed by IHC performed locally or by central laboratory testing. ***Expansion Cohort 10 (NSCLC Activation/Maintenance Dosing): PD-1/L1 Inhibitor Pretreated (100 mg 1Q3W × 2 cycles; then 500 mg once every 6 weeks [1Q6W])*** • Subjects with NSCLC who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of 1 treatment line) for metastatic disease with radiographic disease progression on or after last prior treatment. • Subjects with NSCLC of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment. • Subjects should have received platinum-based therapy (or alternative chemotherapy due to platinum ineligibility, eg, a gemcitabine-containing regimen). • Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor approval is required for subjects with a BOR of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks. • Local results from the most recent PD-L1 test must be provided prior to enrollment. If local PD-L1 test results are unavailable, sponsor approval for enrollment is required. • Subjects must have a PD-L1 expression result from the central laboratory available prior to C1D1 from a fresh tumor sample, which is obtained by core-needle biopsy (aspirates are not acceptable) and is taken after failure/stop of last prior treatment. • Tumor demonstrates PD-L1 expression in ≥1% of tumor cells (TPS ≥1%) as assessed by IHC determined by central laboratory testing. ***Expansion Cohorts EC12 and EC13 (NSCLC Treatment-Naive for Metastatic Disease: GEN1046 in Combination with Pembrolizumab and Platinum-based Chemotherapy)*** • Subjects with non-squamous or squamous metastatic NSCLC who have received no prior systemic treatment regimens for metastatic disease. Subjects must not have received prior treatment with a PD-1/L1 inhibitor. Note: o Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to the start of the trial drug. o Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 6 months prior to the start of the trial drug. • Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK

translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.

- If a local result from the most recent PD-L1 test exists, it must be provided prior to enrollment.
- All subjects must provide a mandatory formalin fixed paraffin embedded (FFPE) tumor sample that is obtained before C1D1 and originates from the metastatic stage of the cancer for retrospective central biomarker evaluation. The tumor tissue should ideally be from the same block of tumor used for local PD-L1 testing, if applicable. Documentation of the tumor sample shipment (ie, airway bill) must be submitted to the sponsor prior to administration of the first dose of GEN1046. If it is not feasible to meet these requirements, the sponsor medical monitor's approval is required prior to enrollment.

For Both Dose Escalation and Expansion

- Subject must have measurable disease according to RECIST 1.1.
- Subject must have Eastern Cooperative Oncology Group 0-1.
- Subject must have organ and bone marrow function as follows:
- Bone marrow/hematological function:
  - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
  - Hemoglobin ≥9.0 g/dL
  - Platelet count $\geq 100 \times 10^9$/L
- Liver function:
  - Total bilirubin ≤ upper limit of normal (ULN)
  - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≤1.5 × ULN
  - Albumin ≥30 g/L
- Coagulation status:
  - Prothrombin time (PT)/International normalized ratio (INR) ≤1.5
  - Activated partial thromboplastin time (aPTT) ≤1.5 × ULN (without anticoagulation therapy)
  - Subjects receiving anticoagulant therapies should have the PT and aPTT within the therapeutic range of intended use of anticoagulants
- Renal function:
  - Glomerular filtration rate ≥45 mL/min/1.73 m^2
- Biopsy requirements are as follows:
  - In the dose escalation part: all subjects must provide a tumor tissue sample (FFPE blocks/slides) from archival tissue or fresh biopsy collected before C1D1, preferably derived from advanced disease stage.
  - In the expansion part for cohorts with all-comers populations (EC1 to EC7 and EC9): all subjects must provide a mandatory fresh biopsy (FFPE blocks/slides) which contains tumor tissue and is taken after failure/stop of last prior treatment and prior to the first GEN1046 infusion. Documentation of the fresh FFPE biopsy collection must be submitted to the sponsor as a part of the eligibility package prior to administration of first dose of GEN1046. Furthermore, the latest available archival tumor tissue sample, which has been taken before failure/stop of last prior treatment, should be collected if available.
  - In the expansion part for EC8: subjects must have a PD-L1 expression result (TPS ≥1% or ≥1% TC) available prior to C1D1 from a tumor sample from the metastatic stage of the cancer. Tumor PD-L1 expression can be determined by the sponsor-designated central laboratory CCI [redacted] or per site local assessment with CCI [redacted] PD-L1 CCI

	CCI assay used per manufacturer's instructions. In addition, all subjects must provide a FFPE tumor sample from the time metastatic disease was diagnosed. This should ideally be from the same block of tumor used for local PD-L1 testing, if applicable. - In the expansion part for EC11: subjects must have a PD-L1 expression result (TPS ≥1% or ≥1% TC) available prior to C1D1 from a tumor sample from the metastatic stage of the cancer. Tumor PD-L1 expression can be determined by the sponsor-designated central laboratory CCI or per site local assessment with CCI PD-L1 CCI assay used per manufacturer's instructions. In addition, all subjects should provide a FFPE tumor sample from the time metastatic disease was diagnosed. This should ideally be from the same block of tumor used for local PD-L1 testing, if applicable. - In the expansion part for EC10: subjects must have a PD-L1 expression result (TPS ≥1%) from the central laboratory available prior to C1D1 from a fresh FFPE tumor sample which is obtained by core-needle biopsy (aspirates are not acceptable) and is taken after failure/stop of last prior treatment. Furthermore, the latest available archival tumor tissue sample, which has been taken before failure/stop of last prior treatment, should be collected if available. - All tumor samples for central biomarker evaluation (for all applicable cohorts) and tumor samples used for local PD-L1 testing (EC8 and EC11 only) must be of sufficient histological quality and have preserved tissue architecture (ie, core-needle biopsies, histological punctures, biopsies performed with mini-forceps, resections are accepted). The following samples are not acceptable for this trial: fine needle aspirates, cell blocks, cell pellets, clots, bone marrow or decalcified bone tissue, and any cytological specimens (smears, brushings, washings, lavages, and effusions). Tissue samples should not have been previously irradiated. FFPE tissue blocks are preferred to slides. In case it is not feasible to meet the tumor tissue requirements, the sponsor medical monitor's approval for enrollment is needed.
Key Exclusion Criteria	• Subject has uncontrolled intercurrent illness, including but not limited to: • Ongoing or active infection requiring intravenous (IV) treatment with anti-infective therapy that has been administered less than 2 weeks prior to first dose, or any ongoing systemic inflammatory condition requiring further diagnostic work-up or management during screening. • Symptomatic congestive heart failure (Grade III or IV as classified by the New York Heart Association), unstable angina pectoris, or cardiac arrhythmia. • Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management. • Ongoing or recent (within 1 year) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs). ***Note: The following conditions are not exclusionary:*** childhood asthma that has resolved, residual hypothyroidism that required only hormone replacement or psoriasis that does not require systemic treatment. • Subjects with a history of grade 3 or higher irAEs that led to treatment discontinuation of a prior immunotherapy treatment should be

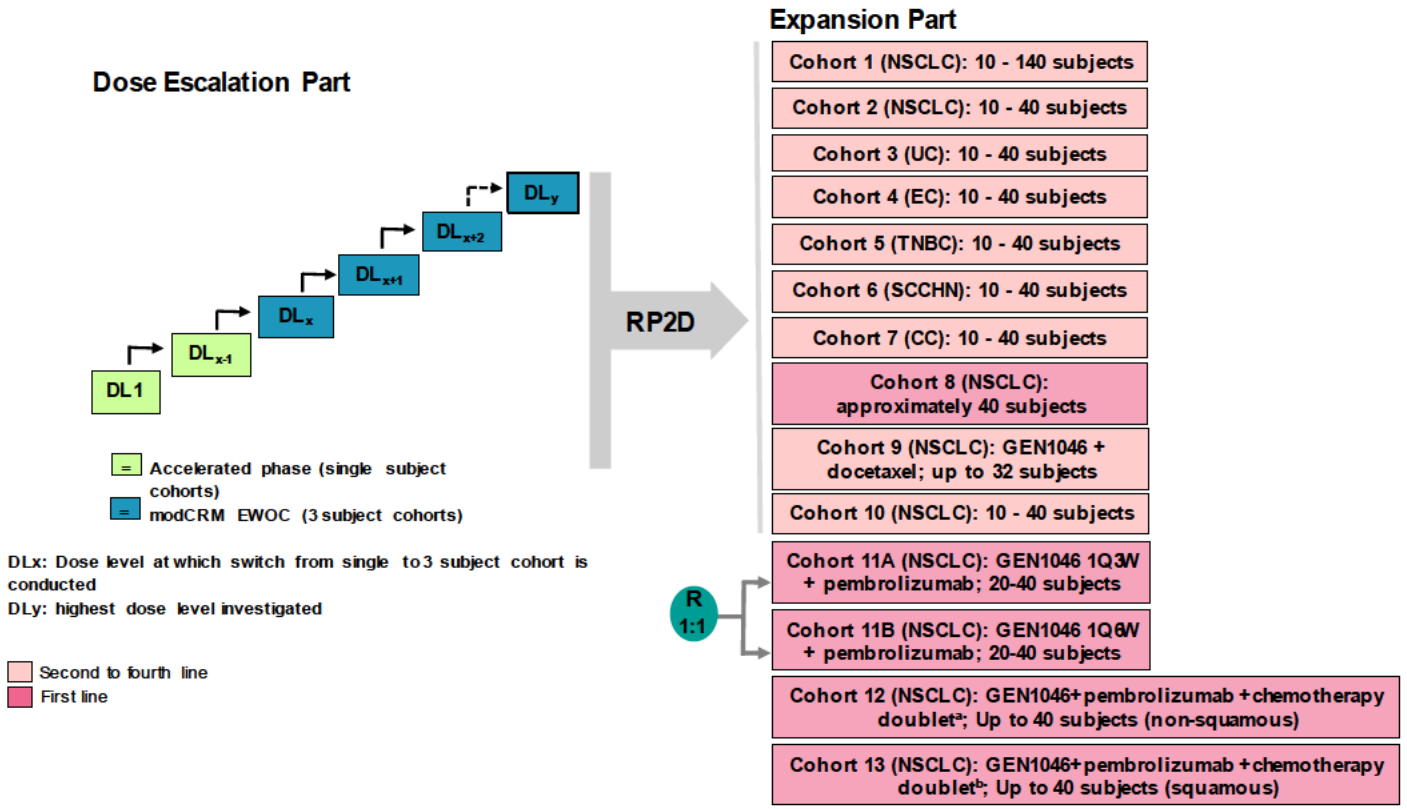
	excluded. Subjects with irAEs below grade 3 that led to discontinuation should be discussed with the sponsor. • Subjects with a prior history of myositis, Guillain-Barré syndrome, or myasthenia gravis of any grade are excluded. • History of chronic liver disease or evidence of hepatic cirrhosis. • History of non-infectious pneumonitis that has required steroids or currently has pneumonitis. • History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of GEN1046. • Serious, non-healing wound, skin ulcer (of any grade), or bone fracture. • CCI [redacted] • All subjects should undergo a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain to document new or existing CNS lesions. • Any history of intracerebral arteriovenous malformation, cerebral aneurysm, spinal cord compression (from disease), carcinomatous meningitis, or stroke (within the last 6 months) will be excluded. Transient ischemic attack >1 month prior to screening is allowed. • Subjects with newly identified or known unstable or symptomatic CNS metastases will be excluded. Subjects with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression for at least 28 days from the radiological diagnosis of brain metastases by repeat imaging that should be performed during trial screening). Subjects should be clinically stable and should not be undergoing acute corticosteroid therapy or steroid taper or have received stereotactic radiation or whole-brain radiation within 14 days prior to C1D1. Chronic steroid therapy is acceptable provided that the dose is stable for the last 14 days prior to C1D1 (≤10 mg prednisone daily or equivalent). Note that radiotherapy is not allowed 14 days prior to first dosing and that the irradiated lesion cannot be used for efficacy assessment. • Prior therapy: • Radiotherapy within 14 days prior to first GEN1046 administration or received lung radiation therapy of >30 Gy within 6 months of the first dose of trial treatment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. Note: Palliative radiotherapy will be allowed. • Unless otherwise noted below, treatment with an anti-cancer agent (within 28 days or after at least 5 half-lives of the drug, whichever is shorter), prior to GEN1046 administration. Accepted exceptions are bisphosphonates (eg, pamidronate, zoledronic acid, etc) and denosumab. • Subject has received any investigational agent (including an investigational vaccine[s]) or used an invasive investigational medical device within 28 days before the planned first dose of GEN1046 or is currently enrolled in an interventional trial. • Prior treatment with live, attenuated vaccines within 3 weeks prior to initiation of GEN1046 treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live

	attenuated vaccines and are not allowed. Experimental and/or non-authorized SARS-CoV-2 vaccinations are not allowed. • Chronic systemic immunosuppressive corticosteroid doses, ie, prednisone >10 mg daily or a cumulative dose >150 mg prednisone within 14 days before the first GEN1046 administration. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted. • Have received granulocyte colony stimulating factor or granulocyte/macrophage colony stimulating factor support 4 weeks prior to first GEN1046 administration or being chronically transfusion dependent. • History of ≥ grade 3 allergic reactions to monoclonal antibody therapy as well as known or suspected allergy or intolerance to any agent given in the course of this trial. • Subjects who discontinued treatment due to disease progression within the first 6 weeks of a CPI containing treatment. • Prior treatment with a 4-1BB (CD137) targeted agent. • Prior treatment with a T-cell agonist or anti-cytotoxic T lymphocyte-associated protein 4 targeted agent within 12 weeks prior to the initiation of treatment. • Toxicities from previous anti-cancer therapies that have not resolved to baseline levels or to grade 1 or less with the exception of alopecia, anorexia, vitiligo, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy. Anorexia, hyperthyroidism, hypothyroidism, and peripheral neuropathy must have recovered to ≤ grade 2. • Known past or current malignancy other than inclusion diagnosis, except for: • Cervical carcinoma of Stage 1B or less. • Non-invasive basal cell or squamous cell skin carcinoma. • Non-invasive, superficial bladder cancer. • Prostate cancer with currently undetectable PSA. • Breast cancer in BRACA1 or BRACA2 positive ovarian cancer subject (not applicable for breast cancer expansion cohort). • Any curable cancer with a complete response of >2 years duration.
Investigational Therapy Dose Escalation and Expansion Cohorts EC1-EC7, EC8, EC10	Dose Escalation: GEN1046 monotherapy at 7 main dose levels: 25, 80, 200, 400, 800, 1200, and 1600 mg including the potential for intermediate dose levels. GEN1046 will be administered in cycles of 21 days. Expansion: GEN1046 100 mg monotherapy will be administered 1Q3W for EC1 to EC7, ie, in cycles of 21 days. For EC8 and EC10, GEN1046 will be administered 100 mg 1Q3W × 2 cycles; then 500 mg 1Q6W for remaining cycles.
Investigational Therapy Expansion Cohort EC9	GEN1046 at 100 mg, in combination with docetaxel, 1Q3W via IV infusion on Day 1 of each 21-day cycle until PD or unacceptable toxicity. Docetaxel will be administered at a dose of 55 mg/m^2 to the first 6 subjects, and if deemed a safe dose in combination with GEN1046, additional subjects will be treated with 75 mg/m^2 for further evaluation of the combination.
Investigational Therapy Expansion Cohorts EC11A and EC11B	Subjects will be randomized to either EC11A or EC11B, to receive GEN1046 100 mg 1Q3W in combination with pembrolizumab 200 mg 1Q3W or GEN1046 100 mg 1Q6W in combination with pembrolizumab 400 mg 1Q6W. CCI [redacted] CCI [redacted] after the regimen has been assessed as safe in a preliminary safety run-in. Treatment will be administered via IV infusion on Day 1 of each 21-day or 42-day cycle, respectively, until PD or unacceptable toxicity CCI [redacted].

Investigational Therapy Expansion Cohorts EC12 and EC13	In EC12 (non-squamous 1L NSCLC): Subjects will receive GEN1046 100 mg 1Q3W in addition to pembrolizumab 200 mg 1Q3W + platinum-based chemotherapy doublet: • pemetrexed 500 mg/m^2 1Q3W • +cisplatin 75 mg/m^2 1Q3W OR carboplatin AUC 5 mg/mL/min 1Q3W for 4 cycles. CCI [redacted] In EC13 (squamous 1L NSCLC): Subjects will receive GEN1046 100 mg 1Q3W in addition to pembrolizumab 200 mg 1Q3W + platinum-based chemotherapy doublet: • carboplatin AUC 6 mg/mL/min 1Q3W • +paclitaxel 200 mg/m^2 1Q3W (Day 1) OR nab-paclitaxel 100 mg/m^2 once (1 dose) every week (1Q1W) (Days 1, 8, and 15) for 4 cycles. CCI [redacted]
Statistics	In dose escalation, MTD and/or RP2D will be determined using a modified Continuous Reassessment Method and Escalation with Overdose Control design. The cohort expansion will be conducted in up to 6 tumor types using the Bayesian predictive probability of success approach with a maximum sample size of 40 per cohort for EC2 through EC8 and EC10, EC12, and EC13. EC1 may enroll up to 140 subjects if the benefit-risk assessment is favorable. The docetaxel combination cohort (EC9) will follow the 6 + 6 design and be evaluated accordingly; a maximum sample size of 32 is planned for EC9. Up to 40 subjects will be randomized and allocated to either EC11A or EC11B (20 in each) with the possibility to expand to 80 subjects in total. EC11, EC12, and EC13 will have a safety run-in before expansion. Adverse events will be presented using summary statistics. Individual curves of plasma concentration for GEN1046 will be presented for all subjects. PK parameters will be calculated based on non-compartmental methods and will be calculated separately. RECIST v1.1 will be used to define response. Summaries of objective response and disease control will be presented by dose cohort/indication and total. iRECIST will also be used to assess objective response and disease control. PFS, OS, and DoR will be summarized using survival analysis methods.

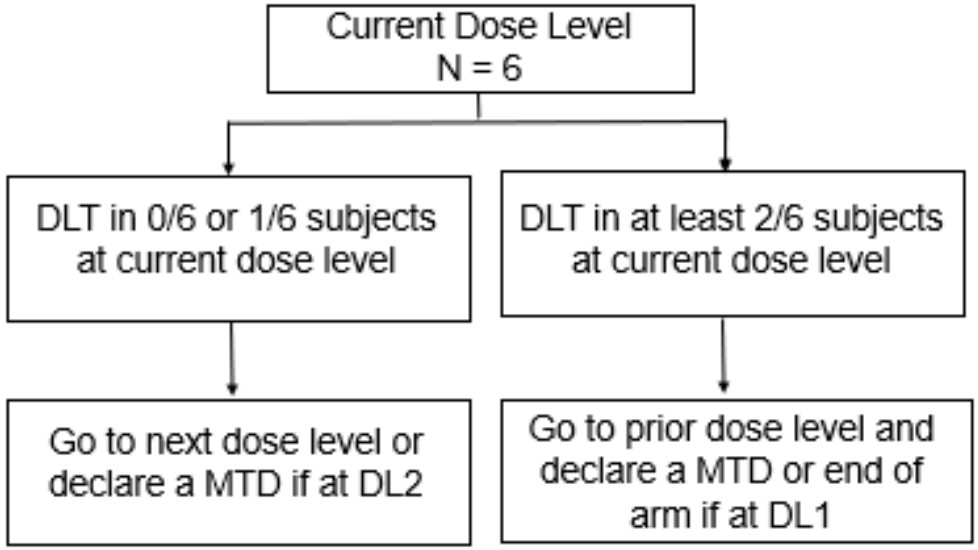
1.2 Schema

Figure 1-1 Overview of Trial Design



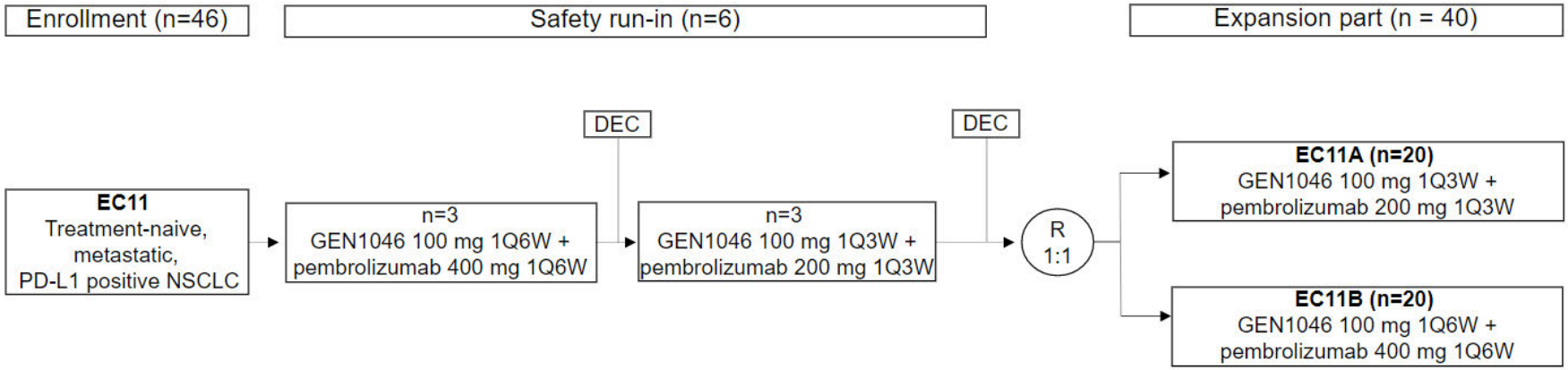
1Q3W = once (1 dose) every 3 weeks; 1Q6W = once (1 dose) every 6 weeks; CC = cervical cancer; EC = endometrial cancer; NSCLC = non-small cell lung cancer; RP2D = recommended phase 2 dose; SCCHN = squamous cell carcinoma of the head and neck; TNBC = triple-negative breast cancer; UC = urothelial carcinoma.
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 1-2 Safety Run-In Escalation Design – EC9 – Docetaxel Combination



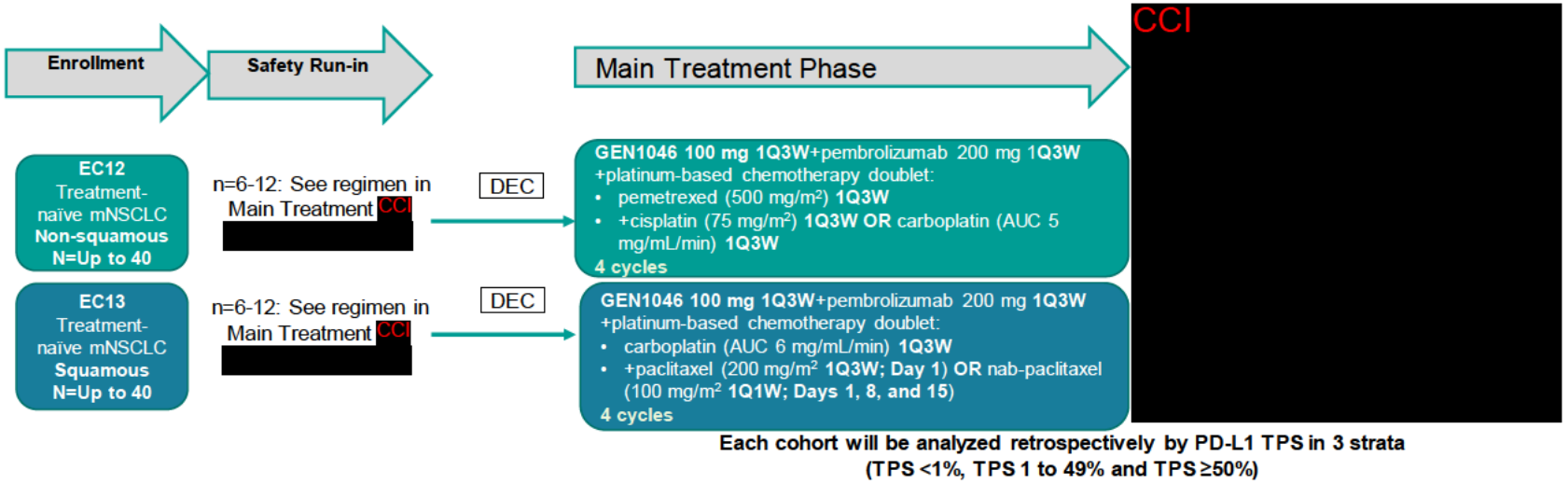
DL = dose level; DLT = dose-limiting toxicity; EC = expansion cohort; MTD = maximum tolerated dose.

Figure 1-3 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 1-4 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.

1.2.1 Expansion Cohorts Table

Table 1-1 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	3a (platinum eligible)	Prior CPI treatment	GEN1046 100 mg 1Q3W
			3b (platinum ineligible)		
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/TC 1% to 49%])	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/TC ≥50%])		
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
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

Cohort No.	n	Cancer Type	Subcohort	Prior Treatment	Trial Treatment
EC11[redacted] (GEN1046 in combination with pembrolizumab)	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 (for pembrolizumab 200 mg 1Q3W up to 35 cycles; total of 2 years)
EC11[redacted] (GEN1046 in combination with pembrolizumab)	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 (for pembrolizumab 400 mg 1Q6W up to 18 cycles; total of 2 years)
EC12 (non-squamous; GEN1046 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]
EC13 (squamous; GEN1046 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 CCI [redacted] TNBC=triple-negative breast cancer; TPS=tumor proportion score CCI [redacted] UC=urothelial carcinoma.

PLEASE NOTE: Any elements in the protocol that are only applicable to sites in certain regions are clearly marked as such in Table 17-2 and are not applicable to sites in other regions.

1.3 Schedule of Activities

Section	Schedule of Activities
1.3.1	Schedule of Activities – Dose Escalation
1.3.2	Schedule of Activities – Expansion
1.3.3	Biomarker Assessments – Dose Escalation and Expansion
1.3.4	Post-Primary Analysis Schedule of Activities – All Subjects

1.3.1 Schedule of Activities – Dose Escalation

Table 1-2 lists all of the assessments in dose escalation and indicates with an "X" the visits when the assessments are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Table 1-3 shows the timing of the pharmacokinetic (PK) and electrocardiogram (ECG) assessments for dose escalation, Table 1-4 shows the timing of the anti-drug antibody (ADA) sampling, and Table 1-5 shows the timing for measurement of vital signs in relation to infusions.

Table 1-2 Visit Evaluation Schedule – Dose Escalation

Treatment Cycle (C)	Screening	Cycle 1-Cycle 2					Cycle 3-Cycle 4			Cycle 5-Cycle X	Treatment discontinuation[1]	Safety follow-up 1[1]	Safety follow-up 2[1]	Survival follow-up[12]	UNS
Day/Week	**≤21 days prior to Visit C1 (1d)**	**1d**	**2d**	**3d**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[2]**	**-**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
Informed consent[16]	X														
Eligibility criteria	X														
Demographics	X														
Medical history[3]	X														
Height	X														
Body weight	X	X					X			X	X				
Physical examination	X	X			X[10]	X[10]	X	X[10]	X[10]	X	X	X			X[8, 10,11]
Vital signs[4]	X	X	X		X	X	X	X[10]	X[10]	X	X	X			X[8]
ECG	X	Please refer to Section 9.4.3 and Table 1-3 for details on ECG assessments													
CT/MRI scan	X[5]	Refer to Section 9.2 for details on Imaging assessments[6]													
ECOG performance status	X	X					X			X	X	X			X[8]
Adverse events[3,17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]	X[8]
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X		X[8]
GEN1046 administration		X					X			X[11]					
End of treatment											X				
New anti-cancer treatment											X	X	X	X	
Survival follow-up														X[12]	
LABORATORY ASSESSMENTS															
Hematology	X[13]	X[14]	X[15]		X[15]	X[15]	X[14]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]		X[8]
Biochemistry[18]	X[13]	X[14]	X[15]		X[15]	X[15]	X[14]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]		X[8]
Coagulation factors	X[13]	X[14]					X[14]			X[14]	X[15]	X[15]	X[15]		X[8]
Endocrine[7]	X[13]	X[14]					X[14]			X[14]					X[8]
Urinalysis	X[13]						X[14]			X[14]	X[15]	X[15]	X[15]		X[8]
Pregnancy test	X[13]						X[14]			X[14]	X[15]	X[15]	X[15]		X[8]
Hepatitis B	X[13]										X[15]				X[8]

Treatment Cycle (C)	Screening	Cycle 1-Cycle 2					Cycle 3-Cycle 4			Cycle 5-Cycle X	Treatment discontinuation[1]	Safety follow-up 1[1]	Safety follow-up 2[1]	Survival follow-up[12]	UNS
Day/Week	**≤21 days prior to Visit C1 (1d)**	**1d**	**2d**	**3d**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[2]**	**-**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
PK/ADA sampling	Refer to Section 9, Table 1-3, and Table 1-4 for details of PK/ADA (immunogenicity) samplings														
Tumor tissue biomarkers	Refer to Table 1-18 for detailed biomarker assessment schedule														

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities).
ADA=anti-drug antibody; AE=adverse event; beta-hCG=beta-human chorionic gonadotropin; C1D1=Cycle 1 Day 1; CT=computed tomography; d=day(s); ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; iRECIST=immune Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic(s); SAE=serious adverse event; SCCHN=squamous cell carcinoma of the head and neck; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; UNS=Unscheduled.

1 If the subject shows PD or confirmed PD (as per iRECIST), starts new anti-cancer treatment, or withdraws from treatment due to another reason, the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of GEN1046. If the subject initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment (see Section 8.4).
2 Visit window (+3d) applies to C2D1 only.
3 Non-serious AEs and SAEs must be reported from first GEN1046 dose until 60 days after last dose of trial treatment (Section 10.2.1).
4 Temperature, blood pressure, and heart rate according to Section 9.4 and Table 1-5 on GEN1046 administration days. On days when GEN1046 is not administered, vital signs only need to be obtained once any time during the visit.
5 All subjects will have a CT scan with contrast or MRI of thorax, abdomen, and pelvis during screening. Head and neck imaging is also required for subjects with SCCHN. Imaging of the pelvis is not required for subjects with SCCHN but is strongly recommended. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial. If there is suggestion of brain metastases/tumors, a CT scan or MRI of the head and neck will be performed within 21 days prior to the C1D1 visit. Scans that exceed the 21-day window may be used for trial enrollment with sponsor approval.
6 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 disease progression, then a subsequent imaging assessment should be performed within 4-7 weeks to confirm progression. Refer to Section 9.2.2 for iRECIST imaging and treatment guidelines.
7 TSH, T3, and T4 will only be measured at screening, C2D1 (or up to 3 days before C2D1), and on Day 1 of every even cycle thereafter (or up to 3 days before the respective Day 1).
8 Only if relevant.
9 Suspected trial treatment related SAEs only.
10 A physical exam and vital signs should only be performed as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator.
11 Subjects who experience a delay in the administration of GEN1046 should return to the clinic at least every 3 weeks (±3 days) and an unscheduled visit should be performed and reported in the eCRF. Unscheduled visit assessments should be performed at the investigator's discretion.
12 Survival follow-up visits may be performed as telephone, email, or visit.
13 All central and local labs at the screening visit must be obtained within 7 days prior to C1D1 (with the exception of hepatitis B sample, which may be obtained earlier). Hematology, chemistry, endocrine, serum (beta-hCG) pregnancy, and hepatitis B will be performed centrally. Coagulation factors and urinalysis will be performed locally.
14 Local and central laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before for Cycle 2 and beyond. Every effort should be made to obtain local and central labs on the same day. Hematology, chemistry, and endocrine labs should be obtained centrally. Hematology, chemistry, coagulation factors, urine pregnancy, and urinalysis should be performed locally.

15 Central labs should be obtained for hematology and biochemistry on Day 2, Day 8, Day 15, treatment discontinuation, and the 30-day and 60-day safety follow-up visits. Hepatitis B should also be obtained centrally at the treatment discontinuation visit. Coagulation factors, urine pregnancy, and urinalysis should always be performed locally.
16 Informed consent may be obtained prior to the screening period. However, C1D1 should be performed within 35 days after signature of informed consent.
17 CCI
18 CCI

Table 1-3 PK and ECG Sampling in Dose Escalation

Treatment Cycle (C)	**Screening**	**Cycle 1- Cycle 2**					**Cycle 3- Cycle X**	**Treatment Discontinu-ation**	**SFU1**	**SFU2**	**UNS**
Day (d)	**≤21 days prior to Visit C1 (1d)**	**1d**	**2d[a]**	**3-5d**	**8d**	**15d**	**1d[b]**	**-**	**30 days after last dose**	**60 days after last dose**	**-**
Before infusion (on infusion days)	1[c]	3	3	3	3	3	3	1	1	1	1[d]
End of infusion (+15 minutes)		3									
End of infusion +2 hours (±15 minutes)		3					3				
End of infusion + 4 hours (±30 minutes)		3									

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and PK sample collection will stop. ECGs will be performed as clinically indicated.
1=single ECG assessment; 3=triplicate ECG assessments; ECG=electrocardiogram; PK=pharmacokinetic(s); SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.
[a] Time window for the Day 2 sample in the dose escalation is 24 hours ±2 hours after the end of infusion on Day 1.
[b] PK and ECG must be obtained Cycle 3, Cycle 5, Cycle 7, and every 4 cycles thereafter (ie, Cycles 3, 5, 7, 11, 15, etc).
[c] ECG assessment only. PK sample should not be collected.
[d] Optional.

Table 1-4 ADA Sampling in Dose Escalation

Treatment Cycle	**Cycle 1- Cycle 2**	**Cycle 3- Cycle X**	**Treatment Discontinuation**	**SFU1**	**SFU2**	**UNS**
Day (d)	**1d**	**1d**	**-**	**30 days after last dose**	**60 days after last dose**	**-**
Before infusion (on infusion days)	X	X[a]	X	X	X	X[b]

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and ADA sample collection will stop.
ADA=anti-drug antibody; SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.
[a] Cycle 3, Cycle 5, Cycle 7, and every 4 cycles thereafter (ie, Cycles 3, 5, 7, 11, 15, etc).
[b] Optional.

Table 1-5 Vital Signs During Dose Escalation

Pre-infusion (up to 30 min before infusion)
15 min after start of infusion (±5 min)[*]
At the end of infusion (±5 min)
30 min after end of infusion (±5 min)
1 hour after end of infusion (±10 min)
2 hours after end of infusion (±10 min)

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities).
[*] If infusion lasts for more than 60 minutes, vital signs should be assessed every 15 minutes (±5 minutes) for the remaining duration of the infusion.

1.3.2 Schedule of Activities – Expansion

The following tables list assessments to be performed in the expansion and indicate with an "X" the visit when the assessments are performed. All data obtained from these assessments must be supported in the subject's source documentation.

- Table 1-6 Visit Evaluation Schedule – Expansion Cohorts EC1-EC7 and EC9 (Docetaxel Combination)
- Table 1-7 Visit Evaluation Schedule – Expansion Cohorts EC8 and EC10, NSCLC Activation/Maintenance Dosing
- Table 1-8 Visit Evaluation Schedule – Expansion Cohort EC11A (1Q3W) (Pembrolizumab Combination)
- Table 1-9 Visit Evaluation Schedule – Expansion Cohort EC11B (1Q6W) (Pembrolizumab Combination)
- Table 1-10 Visit Evaluation Schedule – Expansion Cohort EC12 (Combination Therapy With GEN1046 + Pembrolizumab + Platinum-based Chemotherapy [Pemetrexed + Cisplatin **OR** Carboplatin])
- Table 1-11 Visit Evaluation Schedule – Expansion Cohort EC13 (Combination Therapy With GEN1046 + Pembrolizumab + Platinum-based Chemotherapy [Carboplatin + Paclitaxel **OR** Nab-paclitaxel])
- Table 1-12 PK and ADA Sampling in Expansion Cohorts EC1-EC7 and EC9 (Docetaxel Combination)
- Table 1-13 PK and ADA Sampling in Expansion Cohorts EC8 and EC10, NSCLC Activation/Maintenance Dosing
- Table 1-14 GEN1046 PK and ADA Sampling in Expansion Cohort EC11A NSCLC GEN1046 in Combination with Pembrolizumab with 1Q3W Dosing
- Table 1-15 GEN1046 PK and ADA Sampling in Expansion Cohort EC11B NSCLC GEN1046 in Combination with Pembrolizumab with 1Q6W Dosing
- Table 1-16 GEN1046 PK and ADA Sampling in Safety Run-in and Expansion Cohorts EC12 and EC13 (GEN1046 in Combination with Pembrolizumab and Platinum-based Chemotherapy Doublets)
- Table 1-17 Vital Signs During Expansion (All Cohorts)

Table 1-6 Visit Evaluation Schedule – Expansion Cohorts EC1-EC7 and EC9 (Docetaxel Combination)

Treatment Cycle (C)	**Screening**	**Cycle 1-Cycle 2**					**Cycle 3-Cycle 4**			**Cycle 5-Cycle X**	**Treatment discontin-uation[1]**	**Safety follow-up 1[1]**	**Safety follow-up 2[1]**	**Survival follow-up[12]**	**Unscheduled**
Day (d)/Week	**≤ 21 days prior to Visit C1 (1d)**	**1d**	**2d**	**3d**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[2]**	**-**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
Informed consent[16]	X														
Eligibility criteria	X														
Demographics	X														
Medical history[3]	X														
Height	X														
Body weight	X	X					X			X	X				
Physical examination	X	X			X[10]	X[10]	X	X[10]	X[10]	X	X	X			X[8, 10,11]
Vital signs[4]	X	X	X		X	X	X	X[10]	X[10]	X	X	X			X[8]
ECG	X	X[18,19]					X[18,19]			X[18,19]	X	X	X		
CT/MRI scan	X[5]	Refer to Section 9.2 for details on Imaging assessments[6]													
ECOG performance status	X	X					X			X	X	X			X[8]
Adverse events[3,20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]	X[8]
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X		X[8]
GEN1046 administration		X					X			X[11]					
Docetaxel combination (Cohort EC9) Docetaxel administration[17]		X					X			X[17]					
End of treatment											X				
New anti-cancer treatment											X	X	X	X	
Survival follow-up														X[12]	
LABORATORY ASSESSMENTS															
Hematology	X[13]	X[14]	X[15]		X[15]	X[15]	X[14]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]		X[8]
Biochemistry[21]	X[13]	X[14]	X[15]		X[15]	X[15]	X[14]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]		X[8]
Coagulation factors	X[13]	X[14]					X[14]			X[14]	X[15]	X[15]	X[15]		X[8]
Endocrine[7]	X[13]	X[14]					X[14]			X[14]					X[8]
Urinalysis	X[13]						X[14]			X[14]	X[15]	X[15]	X[15]		X[8]

Treatment Cycle (C)	Screening	Cycle 1-Cycle 2					Cycle 3-Cycle 4			Cycle 5-Cycle X	Treatment discontin-uation[1]	Safety follow-up 1[1]	Safety follow-up 2[1]	Survival follow-up[12]	Unscheduled
Day (d)/Week	**≤ 21 days prior to Visit C1 (1d)**	**1d**	**2d**	**3d**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[2]**	**-**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
Pregnancy test	X[13]	X[14]					X[14]			X[14]	X[15]	X[15]	X[15]		X[8]
Hepatitis B	X[13]										X[15]				X[8]
PK/ADA sampling	Refer to Section 9 and Table 1-12 for details of PK/ADA (immunogenicity) samplings														
Tumor tissue biomarkers	Refer to Table 1-18 for detailed biomarker assessment schedule														

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities).
1Q3W=1 dose every 3 weeks; ADA=anti-drug antibody; AE=adverse event; beta-hCG=beta-human chorionic gonadotropin; C1D1=Cycle 1 Day 1; CT=computed tomography; EC=expansion cohort; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; iRECIST=immune Response Evaluation Criteria in Solid Tumors; IV=intravenous; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic(s); SAE=serious adverse event; SCCHN=squamous cell carcinoma of the head and neck; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone.

1 If the subject shows PD or confirmed PD (as per iRECIST), starts new anti-cancer treatment, or withdraws from treatment due to another reason, the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of trial treatment. If the subject initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment (see Section 8.4).
2 Visit window (+3d) applies to C2D1 only.
3 Non-serious AEs and SAEs must be reported from first GEN1046 dose until 60 days after last dose of trial treatment (Section 10.2.1).
4 Temperature, blood pressure, and heart rate according to Section 9.4 and Table 1-17 of the protocol on GEN1046 administration days. On days when GEN1046 is not administered, vital signs only need to be obtained once any time during the visit.
5 All subjects will have imaging of brain, thorax, abdomen, and pelvis during screening. Head and neck imaging is always required for subjects with SCCHN. Imaging of the pelvis is not required for subjects with SCCHN but is strongly recommended. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial.
6 On-trial imaging will be performed 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 (unless the investigator elects to continue treatment and follow iRECIST), 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 disease progression, then a subsequent imaging assessment should be performed within 4-7 weeks to confirm progression. Refer to Section 9.2.2 for iRECIST imaging and treatment guidelines.
7 TSH, T3, and T4 will only be measured at screening, C2D1 (or up to 3 days before C2D1), and on Day 1 of every even cycle thereafter (or up to 3 days before the respective Day 1).
8 Only if relevant.
9 Suspected trial treatment-related SAEs only.
10 A physical exam and vital signs should only be performed as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator.
11 Subjects who experience a delay in the administration of trial treatment should return to the clinic at least every 3 weeks (±3 days) and an unscheduled visit should be performed. Unscheduled visit assessments should be performed at the investigator's discretion.
12 Survival follow-up visits may be performed as telephone, email, or visit.
13 All central and local labs at the screening visit must be obtained within 7 days prior to C1D1 (with the exception of hepatitis B sample, which may be obtained earlier). Hematology, chemistry, endocrine, serum (beta-hCG) pregnancy, and hepatitis B will be performed centrally. Coagulation factors and urinalysis will be performed locally.

14 Local and central laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before for Cycle 2 and beyond. Every effort should be made to obtain local and central labs on the same day. Hematology, chemistry, and endocrine labs should be obtained centrally. Hematology, chemistry, coagulation factors, urine pregnancy, and urinalysis should be performed locally.
15 Central labs should be obtained for hematology and biochemistry on Day 2, Day 8, Day 15, treatment discontinuation, and the 30-day and 60-day safety follow-up visits. Hepatitis B should also be obtained centrally at the treatment discontinuation visit. Coagulation factors, urine pregnancy, and urinalysis should always be performed locally.
16 Informed consent may be obtained prior to the screening period. However, C1D1 should be performed within 35 days after informed consent has been obtained.
17 Docetaxel administration in combination with GEN1046 is relevant only for the docetaxel combination cohort. GEN1046 at 100 mg will be administered in combination with docetaxel, 1Q3W via IV infusion on Day 1 of each 21-day cycle until disease progression or until 1 predefined discontinuation of treatment criterion has been met.
18 On infusion days, ECG before infusion and at the end of infusion + 2 hours (±15 minutes).
19 ECG must be obtained at Cycle 1-3, Cycle 5, Cycle 7, and every 4 cycles thereafter.
20 CCI [redacted]
21 CCI [redacted]

Table 1-7 Visit Evaluation Schedule – Expansion Cohorts EC8 and EC10, NSCLC Activation/Maintenance Dosing

Treatment Cycle (C)	Screening	Cycle 1-Cycle 2 (1Q3W)			Cycle 3 (1Q6W)						Cycle 4-Cycle X (1Q6W)		Treatment discontin-uation[1]	Safety follow-up 1[1]	Safety follow-up 2[1]	Survival follow-up[12]	UNS
Day (d)/Week	**≤35 days prior to Visit C1 (1d)**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**22d**	**29d**	**36d**	**1d**	**22d**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[2]**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
Informed consent[16]	X																
Eligibility criteria	X																
Demographics	X																
Medical history[3]	X																
Height	X																
Body weight	X	X			X								X				
Physical examination	X	X	X[10]	X[10]	X						X		X	X			X[8,10,11]
Vital signs[4]	X	X	X	X	X						X		X	X			X[8]
ECG	X	X[17,18]			X[17,18]						X[17,18]		X	X	X		
CT/MRI scan	X[5]	Refer to Section 9.2 for details on Imaging assessments[6]															
ECOG performance status	X	X			X						X		X	X			X[8]
Adverse events[3,19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]	X[8]
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[8]
GEN1046 administration low dose (100 mg) 1Q3W for the first 2 cycles		X															
GEN1046 administration high dose (500 mg) 1Q6W for all cycles starting at Cycle 3					X[11]						X[11]						
End of treatment													X				
New anti-cancer treatment													X	X	X	X	

Treatment Cycle (C)	Screening	Cycle 1-Cycle 2 (1Q3W)			Cycle 3 (1Q6W)						Cycle 4-Cycle X (1Q6W)		Treatment discontin-uation[1]	Safety follow-up 1[1]	Safety follow-up 2[1]	Survival follow-up[12]	UNS
Day (d)/Week	**≤35 days prior to Visit C1 (1d)**	**1d**	**8d**	**15d**	**1d**	**8d**	**15d**	**22d**	**29d**	**36d**	**1d**	**22d**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[2]**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**±3d**	**±3d**	**±3d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
Survival follow-up																X[12]	
LABORATORY ASSESSMENTS																	
Hematology	X[13]	X[14]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]	X[15]		X[8, 21]
Biochemistry[20]	X[13]	X[14]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]	X[15]		X[8, 21]
Coagulation factors	X[13]	X[14]			X[14]			X[15]			X[14]		X[15]	X[15]	X[15]		X[8]
Endocrine[7]	X[13]	X[14]			X[14]			X[15]			X[14]						X[8]
Urinalysis	X[13]				X[14]			X[15]			X[14]		X[15]	X[15]	X[15]		X[8]
Pregnancy test	X[13]	X[14]			X[14]			X[15]			X[14]		X[15]	X[15]	X[15]		X[8]
Hepatitis B	X[13]												X[15]				X[8]
PK/ADA sampling	Refer to Section 9 and Table 1-13 for details of PK/ADA (immunogenicity) samplings																
Tumor tissue (EC8)/ biopsy (EC10), biomarkers	Refer to Table 1-19 for detailed biomarker assessment schedule																

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities).
1Q3W=1 dose every 3 weeks; 1Q6W=1 dose every 6 weeks; ADA=anti-drug antibody; AE=adverse event; beta-hCG=beta-human chorionic gonadotropin; C1D1=Cycle 1 Day 1; CT=computed tomography; EC=expansion cohort; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; iRECIST=immune Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; NSCLC=non-small cell lung cancer; PD=progressive disease; PK=pharmacokinetic(s); SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; UNS=unscheduled.

1 If the subject shows PD or confirmed PD (as per iRECIST), starts new anti-cancer treatment, or withdraws from treatment due to another reason, the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of trial treatment. If the subject initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment (see Section 8.4).
2 Visit window (±3d) applies to C2D1 only.
3 Non-serious AEs and SAEs must be reported from first GEN1046 dose until 60 days after last dose of trial treatment (Section 10.2.1).
4 Temperature, blood pressure, and heart rate according to Section 9.4 and Table 1-17 of the protocol on GEN1046 administration days. On days when GEN1046 is not administered, vital signs only need to be obtained once any time during the visit.
5 All subjects will have imaging of brain, thorax, abdomen, and pelvis during screening. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial.
6 On-trial imaging will be performed 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 (unless the investigator elects to continue treatment and follow iRECIST), 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 disease progression, then a subsequent imaging assessment should be performed within 4-7 weeks to confirm progression. Refer to Section 9.2.2 for iRECIST imaging and treatment guidelines.
7 TSH, T3, and T4 will only be measured at screening, C2D1 (or up to 3 days before C2D1), and on Day 1 of every even cycle thereafter (or up to 3 days before the respective Day 1).

8 Only if relevant.
9 Suspected trial treatment-related SAEs only.
10 A physical exam and vital signs should only be performed as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator.
11 Subjects who experience a delay in the administration of trial treatment should return to the clinic at least every 3 weeks (±3 days) and an unscheduled visit should be performed. Unscheduled visit assessments should be performed at the investigator's discretion.
12 Survival follow-up visits may be performed as telephone, email, or visit.
13 All central and local labs at the screening visit must be obtained within 7 days prior to C1D1 (with the exception of hepatitis B sample, which may be obtained earlier). Hematology, chemistry, endocrine, serum (beta-hCG) pregnancy, and hepatitis B will be performed centrally. Coagulation factors and urinalysis will be performed locally.
14 Local and central laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before for Cycle 2 and beyond. Every effort should be made to obtain local and central labs on the same day. Hematology, chemistry, and endocrine labs should be obtained centrally. Hematology, chemistry, coagulation factors, urine pregnancy, and urinalysis should be performed locally.
15 Central labs should be obtained for hematology and biochemistry on Day 8 (Cycle 1-3), Day 15 (Cycle 1-3), Day 22 (Cycle 3 and beyond; during Cycle 3 only also Days 29 and 36) treatment discontinuation, and the 30-day and 60-day safety follow-up visits. Hepatitis B should also be obtained centrally at the treatment discontinuation visit. Coagulation factors, urine pregnancy, and urinalysis should always be performed locally.
16 Informed consent may be obtained prior to the screening period. However, C1D1 should be performed within 35 days after informed consent has been obtained.
17 On infusion days, ECG before infusion and at end of infusion + 2 hours (±15 minutes).
18 ECG must be obtained at Cycle 1-5, and every 2 cycles thereafter.
19 CCI [redacted]
20 CCI [redacted]
21 CCI [redacted]

Table 1-8 Visit Evaluation Schedule – Expansion Cohort EC11A (1Q3W) (Pembrolizumab Combination)

Treatment Cycle (C)	Screening	Cycle 1-Cycle 4				Cycle 5-Cycle X	Treatment discontinuation[1]	Safety follow-up 1[1]	Safety follow-up 2[1]	Survival follow-up[12]	UNS
Day (d)/Week	**≤35 days prior to Visit C1 (1d)**	**1d**	**3d (only C1 and C2)**	**8d**	**15d**	**1d**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[2]**	**+1d**	**±1d**	**±1d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
Informed consent[16]	X										
Eligibility criteria	X										
Demographics	X										
Medical history[3]	X										
Height	X										
Body weight	X	X					X				
Physical examination	X	X	X[10]	X[10]	X[10]	X	X	X			X[8, 10,11]
Vital signs[4]	X	X		X	X	X	X	X			X[8]
ECG	X	X[17,18]				X[17,18]	X	X	X		
CT/MRI scan	X[5]	Refer to Section 9.2 for details on Imaging assessments[6]									
ECOG performance status	X	X				X	X	X			X[8]
Adverse events[3,20]	X	X	X	X	X	X	X	X	X	X[9]	X[8]
Concomitant medication	X	X	X	X	X	X	X	X	X		X[8]
GEN1046 administration		X[11]				X[11]					
Pembrolizumab administration		X[11]				X[11]					
End of treatment							X				
New anti-cancer treatment							X	X	X	X	
Survival follow-up										X[12]	
LABORATORY ASSESSMENTS											
Hematology	X[13]	X[14]	X[15]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]		X[8, 22]
Biochemistry[21]	X[13]	X[14]	X[15]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]		X[8, 22]
Coagulation factors	X[13]	X[14]				X[14]	X[15]	X[15]	X[15]		X[8]
Endocrine[7]	X[13]	X[14]				X[14]	X[15]	X[15]	X[15]		X[8]
Urinalysis	X[13]	X[19]				X[14]	X[15]	X[15]	X[15]		X[8]
Pregnancy test	X[13]	X[14]				X[14]	X[15]	X[15]	X[15]		X[8]
Hepatitis B	X[13]						X[15]				X[8]
PK/ADA sampling	Please refer to Table 1-14										

Treatment Cycle (C)	Screening	Cycle 1-Cycle 4				Cycle 5-Cycle X	Treatment discontinuation[1]	Safety follow-up 1[1]	Safety follow-up 2[1]	Survival follow-up[12]	UNS
Day (d)/Week	**≤35 days prior to Visit C1 (1d)**	**1d**	**3d (only C1 and C2)**	**8d**	**15d**	**1d**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[2]**	**+1d**	**±1d**	**±1d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
Tumor tissue biomarkers	Please refer to Table 1-20										

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities).
1Q3W=1 dose every 3 weeks; 1Q6W=1 dose every 6 weeks; ADA=anti-drug antibody; AE=adverse event; beta-hCG=beta-human chorionic gonadotropin; C1D1=Cycle 1 Day 1; C2D1=Cycle 2 Day 1; CT=computed tomography; EC=expansion cohort; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; iRECIST=immune Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; NSCLC=non-small cell lung cancer; PD=progressive disease; PK=pharmacokinetic(s); SAE=serious adverse event; SCCHN=squamous cell carcinoma of the head and neck; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; UNS=unscheduled.

1 If the subject shows PD or confirmed PD (as per iRECIST), starts new anti-cancer treatment, or withdraws from treatment due to another reason, the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of trial treatment. If the subject initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment (see Section 8.4).
2 Visit window (±3d) applies to C2D1-C4D1 only.
3 Non-serious AEs and SAEs must be reported from first GEN1046 dose until 60 days after last dose of trial treatment (Section 10.2.1).
4 Temperature, blood pressure and heart rate according to Section 9.4 and Table 1-17 of the protocol on GEN1046 administration days. On days when GEN1046 is not administered, vital signs only need to be obtained once any time during the visit.
5 All subjects will have imaging of brain, thorax, abdomen, and pelvis during screening. Head and neck imaging is always required for subjects with SCCHN. Imaging of the pelvis is not required for subjects with SCCHN but is strongly recommended. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial**.**
6 On-trial imaging will be performed 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 (unless the investigator elects to continue treatment and follow iRECIST), 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 disease progression, then a subsequent imaging assessment should be performed within 4-7 weeks to confirm progression. Refer to Section 9.2.2 for iRECIST imaging and treatment guidelines.
7 TSH, T3, and T4 will only be measured at screening, C2D1 (or up to 3 days before C2D1), on Day 1 of every even cycle thereafter (or up to 3 days before the respective Day 1), and at discontinuation.
8 Only if relevant.
9 Suspected trial treatment related SAEs only.
10 A physical exam and vital signs should only be performed as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator.
11 Subjects who experience a delay in the administration of trial treatment should return to the clinic within 3 weeks (±3 days) and an unscheduled visit should be performed. Unscheduled visit assessments should be performed at the investigator's discretion.
12 Survival follow-up visits may be performed as telephone, email, or visit.
13 All central and local labs at the screening visit must be obtained within 7 days of C1D1 (with the exception of hepatitis B sample, which may be obtained earlier). Hematology, chemistry, endocrine, serum (beta-hCG) pregnancy, and hepatitis B will be performed centrally. Coagulation factors and urinalysis will be performed locally.
14 Local and central laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before for Cycle 2 and beyond. Every effort should be made to obtain local and central labs on the same day. Hematology, chemistry, and endocrine labs should be obtained centrally. Hematology, chemistry, coagulation factors, urine pregnancy, and urinalysis should be performed locally.

15 Central labs should be obtained for hematology and biochemistry on Day 3, Day 8, Day 15 (of relevant cycles), treatment discontinuation, and the 30-day and 60-day safety follow-up visits. Hepatitis B should also be obtained centrally at the treatment discontinuation visit. Coagulation factors, urine pregnancy, and urinalysis should always be performed locally.
16 Informed consent may be obtained prior to the screening period. However, C1D1 should be performed within 35 days after informed consent has been obtained.
17 On infusion days, ECG before infusion and at the end of infusion + 2 hours (± 15 minutes).
18 ECG must be obtained at Cycle 1-3, Cycle 5, Cycle 7, and every 4 cycles thereafter.
19 Urinalysis only on C3D1.
20 CCI [redacted]
21 CCI [redacted]
22 CCI [redacted]

Table 1-9 Visit Evaluation Schedule – Expansion Cohort EC11B (1Q6W) (Pembrolizumab Combination)

Treatment Cycle (C)	Screening	Cycle 1-Cycle 2							Cycle 3-Cycle 4					Cycle 5-Cycle X		Treat-ment discon-ti-nuation[1]	Safety follow -up 1[1]	Safety follow -up 2[1]	Survival follow-up[12]	UNS
Day (d)/Week	≤35 days prior to Visit C1 (1d)	1d	3d	8d	15d	22d	29d	36d	1d	8d	15d	22d	29d	1d	22d	-	30 days after last dose	60 days after last dose	Every 12 weeks after last dose	
Visit window		+3d[2]	+1d	±1d	±1d	+3d	±1d	±1d	±3d	±1d	±1d	±3d	±1d	±3d	±3d	-	+5d	±7d	±14d	
Informed consent[16]	X																			
Eligibility criteria	X																			
Demographics	X																			
Medical history	X																			
Height	X																			
Body weight	X	X				X										X				
Physical examination	X	X	X[10]	X[10]	X[10]	X	X[10]	X[10]	X	X[10]	X[10]	X[10]	X[10]	X	X[10]	X	X			X[8, 10,11]
Vital signs[4]	X	X		X	X	X	X[10]	X[10]	X		X	X[10]	X[10]	X	X[10]	X	X			X[8]
ECG	X	X[17]				X			X[17, 18]					X[17, 18]		X	X	X		
CT/MRI scan	X[5]	Refer to Section 9.2 for details on Imaging assessments[6]																		
ECOG performance status	X	X				X			X			X		X	X	X	X			X[8]
Adverse events[3,20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]	X[8]
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[8]
GEN1046 administration		X[11]							X[11]					X[11]						
Pembrolizumab administration		X[11]							X[11]					X[11]						
End of treatment																X				
New anti-cancer treatment																X	X	X	X	
Survival follow-up																			X[12]	
LABORATORY ASSESSMENTS																				
Hematology	X[13]	X[14]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]		X[8, 22]
Biochemistry[21]	X[13]	X[14]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[14]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]	X[15]		X[8, 22]
Coagulation factors	X[13]	X[14]							X[14]					X[14]		X[15]	X[15]	X[15]		X[8]
Endocrine[7]	X[13]	X[14]							X[14]					X[14]		X[15]	X[15]	X[15]		X[8]
Urinalysis	X[13]	X[19]							X[14]					X[14]		X[15]	X[15]	X[15]		X[8]
Pregnancy test	X[13]	X[14]							X[14]					X[14]		X[15]	X[15]	X[15]		X[8]

Treatment Cycle (C)	**Screening**	**Cycle 1-Cycle 2**							**Cycle 3-Cycle 4**					**Cycle 5-Cycle X**		**Treat-ment disconti-nuation[1]**	**Safety follow -up 1[1]**	**Safety follow -up 2[1]**	**Survival follow-up[12]**	**UNS**
Day (d)/Week	**≤35 days prior to Visit C1 (1d)**	**1d**	**3d**	**8d**	**15d**	**22d**	**29d**	**36d**	**1d**	**8d**	**15d**	**22d**	**29d**	**1d**	**22d**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[2]**	**+1d**	**±1d**	**±1d**	**+3d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	**±1d**	**±3d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
Hepatitis B	X[13]															X[15]				X[8]
PK/ADA sampling	Please refer to Table 1-15																			
Tumor tissue biomarkers	Please refer to Table 1-21																			

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities).
1Q6W=1 dose every 6 weeks; ADA=anti-drug antibody; AE=adverse event; beta-hCG=beta-human chorionic gonadotropin; C1D1=Cycle 1 Day 1; C2D1=Cycle 2 Day 1; CT=computed tomography; EC=expansion cohort; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; iRECIST=immune Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic(s); SAE=serious adverse event; SCCHN=squamous cell carcinoma of the head and neck; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; UNS=unscheduled.

1 If the subject shows PD or confirmed PD (as per iRECIST), starts new anti-cancer treatment, or withdraws from treatment due to another reason, the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of trial treatment. If the subject initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment (see Section 8.4).
2 Visit window (±3d) applies to C2D1 only.
3 Non-serious AEs and SAEs must be reported from first GEN1046 dose until 60 days after last dose of trial treatment (Section 10.2.1).
4 Temperature, blood pressure and heart rate according to Section 9.4 and Table 1-17 of the protocol on GEN1046 administration days. On days when GEN1046 is not administered, vital signs only need to be obtained once any time during the visit.
5 All subjects will have imaging of brain, thorax, abdomen, and pelvis during screening. Head and neck imaging is always required for subjects with SCCHN. Imaging of the pelvis is not required for subjects with SCCHN but is strongly recommended. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial.
6 On-trial imaging will be performed 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 (unless the investigator elects to continue treatment and follow iRECIST), 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 disease progression, then a subsequent imaging assessment should be performed within 4-7 weeks to confirm progression. Refer to Section 9.2.2 for iRECIST imaging and treatment guidelines.
7 TSH, T3, and T4 will only be measured at screening, C2D1 (or up to 3 days before C2D1), on Day 1 of every even cycle thereafter (or up to 3 days before the respective Day 1), and at discontinuation.
8 Only if relevant.
9 Suspected trial treatment-related SAEs only.
10 A physical exam and vital signs should only be performed as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator.
11 Subjects who experience a delay in the administration of trial treatment should return to the clinic within 3 weeks (±3 days) and an unscheduled visit should be performed. Unscheduled visit assessments should be performed at the investigator's discretion.
12 Survival follow-up visits may be performed as telephone, email, or visit.
13 All central and local labs at the screening visit must be obtained within 7 days of C1D1 (with the exception of hepatitis B sample, which may be obtained earlier). Hematology, chemistry, endocrine, serum (beta-hCG) pregnancy, and hepatitis B will be performed centrally. Coagulation factors and urinalysis will be performed locally.

14 Local and central laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before for Cycle 2 and beyond. Every effort should be made to obtain local and central labs on the same day. Hematology, chemistry, and endocrine labs should be obtained centrally. Hematology, chemistry, coagulation factors, urine pregnancy, and urinalysis should be performed locally.
15 Central labs should be obtained for hematology and biochemistry on Day 3, Day 8, Day 15, Day 22, Day 29, Day 36 (of relevant cycles), treatment discontinuation, and the 30 day and 60-day safety follow-up visits. Hepatitis B should also be obtained centrally at the treatment discontinuation visit. Coagulation factors, urine pregnancy, and urinalysis should always be performed locally.
16 Informed consent may be obtained prior to the screening period. However, C1D1 should be performed within 35 days after informed consent has been obtained.
17 On infusion days, ECG before infusion and at the end of infusion + 2 hours (± 15 minutes).
18 ECG must be obtained at Cycle 1-5, and every 2 cycles thereafter.
19 Urinalysis only on C2D1.
20 CCI [redacted]
21 CCI [redacted]
22 CCI [redacted]

Table 1-10 Visit Evaluation Schedule – Expansion Cohort EC12 (Combination Therapy with GEN1046 + Pembrolizumab + Platinum-based Chemotherapy [Pemetrexed + Cisplatin OR Carboplatin])

Treatment Cycle (C)	Screening	Main Treatment Phase Cycles 1-4				CCI Cycles 5-6			CCI Cycles 7-X	Treatment Discontinuation[1]	Safety Follow-up 1[1]	Safety Follow-up 2[1]	Survival Follow-up[2]	UNS
Day/Week	**≤35 days prior to Visit C1 (1d)**	**1d**	**3d[15]**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	-	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	-
Visit window		**+3d[3]**	**+1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	-	**+3d**	**±7d**	**±14d**	-
Informed consent[9]	X	Subjects must sign an informed consent form prior to any trial-specific procedures												
Eligibility criteria	X													
Demographics	X													
Medical history	X													
Height	X													
Body weight	X	X				X[19]			X	X				
Physical examination[5]	X	X				X			X	X	X			X[6]
Vital signs[7]	X	X		X	X	X	X	X	X	X	X			X[6]
ECG	X	X[20, 21]				X[20, 21]			X[20, 21]	X	X	X		
CT/MRI scan	X[17]	Refer to Section 9.2 for details on imaging assessments[18]												
ECOG PS	X	X				X			X	X	X			X[6]
Adverse events[4,22]	X	X	X	X	X	X	X	X	X	X	X	X	X[8]	X[6]
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X		X[6]
GEN1046 administration[14]		X				X			X					
Pembrolizumab administration[14]		X				X			X					
Cisplatin **OR** Carboplatin administration[14]		X												
Pemetrexed administration[14]		X				X			X					
End of treatment										X				
New anti-cancer treatment										X	X	X	X	

Treatment Cycle (C)	Screening	Main Treatment Phase Cycles 1-4				CCI Cycles 5-6			CCI Cycles 7-X	Treatment Discontinuation[1]	Safety Follow-up 1[1]	Safety Follow-up 2[1]	Survival Follow-up[2]	UNS
Day/Week	≤35 days prior to Visit C1 (1d)	1d	3d[15]	8d	15d	1d	8d	15d	1d	-	30 days after last dose	60 days after last dose	Every 12 weeks after last dose	-
Visit window		+3d[3]	+1d	±1d	±1d	±3d	±1d	±1d	±3d	-	+3d	±7d	±14d	-
LABORATORY ASSESSMENTS														
Hematology	X[10]	X[11]	X[12]	X[12]	X[12]	X[11]	X	X	X[11]	X[12]	X[12]	X[12]		X[6, 24]
Biochemistry[23]	X[10]	X[11]	X[12]	X[12]	X[12]	X[11]	X	X	X[11]	X[12]	X[12]	X[12]		X[6, 24]
Coagulation factors	X[10]	X[11]				X[11]			X[11]	X[12]	X[12]	X[12]		X[6]
Endocrine[13]	X[10]	X[11]				X[11]			X[11]	X[12]	X[12]	X[12]		X[6]
Urinalysis	X[10]	X[11, 16]				X[11]			X[11]	X[12]	X[12]	X[12]		X[6]
Pregnancy test	X[10]	X[11]				X[11]			X[11]	X[12]	X[12]	X[12]		X[6]
Hepatitis B	X[10]									X[12]				
PK/ADA sampling		Refer to Section 9 and Table 1-16 for details of PK/ADA (immunogenicity) samplings												
Tumor tissue biomarkers		Refer to Table 1-22 for detailed biomarker assessment schedule												

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities).
ADA=anti-drug antibody; AE=adverse event; CT=computed tomography; EC=expansion cohort; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; beta-hCG=beta-human chorionic gonadotropin; iRECIST=immune Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic; PS=performance status; SCCHN=squamous cell carcinoma of the head and neck; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; UNS=unscheduled.

1. If the subject shows PD or confirmed PD (as per iRECIST), starts new anti-cancer treatment, or withdraws from treatment due to another reason, the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of trial treatment. If the subject initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment (see Section 8.4).
2. Survival follow-up may be performed as telephone, email, or on-site visit.
3. Visit window (±3d) applies to C2D1-C4D1 only.
4. Non-serious AEs and SAEs must be reported from first GEN1046 dose until 60 days after last dose of trial treatment (Section 10.2.1).
5. Full complete physical exam at screening. A targeted physical exam should be performed at Day 1 of each cycle as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator.
6. At investigator's discretion, only if clinically indicated.
7. Temperature, blood pressure, and heart rate according to Section 9.4 and Table 1-17 of the protocol on GEN1046 administration days. On days when GEN1046 is not administered, vital signs only need to be obtained once any time during the visit.
8. Suspected trial treatment-related SAEs only.
9. Informed consent may be obtained prior to the screening period. However, C1D1 should be performed within 35 days after informed consent has been obtained.
10. All central and local labs at the screening visit must be obtained within 7 days of C1D1 (with the exception of hepatitis B sample, which may be obtained earlier). Hematology, chemistry, endocrine, serum (beta-hCG) pregnancy, and hepatitis B will be performed centrally. Coagulation factors and urinalysis will be performed locally.
11. Local and central laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before for Cycle 2 and beyond. Every effort should be made to obtain local and central labs on the same day. Hematology, chemistry, and endocrine labs should be obtained centrally. Hematology, chemistry, coagulation factors, urine pregnancy, and urinalysis

should be performed locally.

12. Central labs should be obtained for hematology and biochemistry on Day 3, Day 8, Day 15 (of relevant cycles), treatment discontinuation and the 30-day and 60-day safety follow-up visits. Hepatitis B should also be obtained centrally at the treatment discontinuation visit. Coagulation factors, urine pregnancy, and urinalysis should always be performed locally.
13. TSH, T3, and T4 will only be measured at screening, C2D1 (or up to 3 days before C2D1), on Day 1 of every even cycle thereafter (or up to 3 days before the respective Day 1), and at discontinuation.
14. Subjects who experience a delay in the administration of trial treatment should return to the clinic within 3 weeks (±3 days) and an unscheduled visit should be performed. Unscheduled visit assessments should be performed at the investigator's discretion.
15. The Day 3 visit is required only for Cycles 1 and 2.
16. Urinalysis only on C2D1.
17. All subjects will have imaging of brain, thorax, abdomen, and pelvis during screening. Head and neck imaging is always required for subjects with SCCHN. Imaging of the pelvis is not required for subjects with SCCHN but is strongly recommended. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial.
18. On-trial imaging will be performed 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 (unless the investigator elects to continue treatment and follow iRECIST), 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 disease progression, then a subsequent imaging assessment should be performed within 4-7 weeks to confirm progression. Refer to Section 9.2.2 for iRECIST imaging and treatment guidelines.
19. Only Cycle 5 Day 1.
20. On infusion days, ECG before GEN1046 infusion and at the end of GEN1046 infusion + 2 hours (±15 minutes).
21. ECG must be obtained at Cycles 1-3, Cycle 5, Cycle 7, and every 4 cycles thereafter.
22. CCI [redacted]
23. CCI [redacted]
24. CCI [redacted]

Table 1-11 Visit Evaluation Schedule – Expansion Cohort EC13 (Combination Therapy with GEN1046 + Pembrolizumab + Platinum-based Chemotherapy [Carboplatin + Paclitaxel OR Nab-paclitaxel])

Treatment Cycle	Screening	Main Treatment Phase Cycles 1-4				CCI Cycles 5-6			CCI Cycles 7-X	Treatment Discontinuation[1]	Safety Follow-up 1[1]	Safety Follow-up 2[1]	Survival Follow-up[2]	UNS
Day/Week	**≤35 days prior to Visit C1 (1d)**	**1d**	**3d[15]**	**8d**	**15d**	**1d**	**8d**	**15d**	**1d**	-	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks after last dose**	
Visit window		**+3d[3]**	**+1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	-	**+3d**	**±7d**	**±14d**	
Informed consent[13]	X	Subjects must sign an informed consent form prior to any trial-specific procedures												
Eligibility criteria	X													
Demographics	X													
Medical history	X													
Height	X													
Body weight	X	X				X[19]			X	X				
Physical examination[5]	X	X				X			X	X	X			X[6]
Vital signs[7]	X	X		X	X	X	X	X	X	X	X			X[6]
ECG	X	X[20, 21]				X[20, 21]			X[20, 21]	X	X	X		
CT/MRI scan	X[17]	Refer to Section 9.2 for details on imaging assessments[18]												
ECOG PS	X	X				X			X	X	X			X[6]
Adverse Events[4,23]	X	X	X	X	X	X	X	X	X	X	X	X	X[8]	X[6]
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X		X[6]
GEN1046 administration [14]		X				X			X					
Pembrolizumab administration[14]		X				X			X					
Carboplatin administration[14]		X												
Option 1: Paclitaxel administration[14]		X												
Option 2: Nab-paclitaxel[14]		X		X	X									
End of treatment										X				
New anti-cancer treatment										X	X	X	X	

Treatment Cycle	Screening	Main Treatment Phase Cycles 1-4				CCI Cycles 5-6			CCI Cycles 7-X	Treatment Discontinuation[1]	Safety Follow-up 1[1]	Safety Follow-up 2[1]	Survival Follow-up[2]	UNS
Day/Week	≤35 days prior to Visit C1 (1d)	1d	3d[15]	8d	15d	1d	8d	15d	1d	-	30 days after last dose	60 days after last dose	Every 12 weeks after last dose	
Visit window		+3d[3]	+1d	±1d	±1d	±3d	±1d	±1d	±3d	-	+3d	±7d	±14d	
LABORATORY ASSESSMENTS														
Hematology	X[9]	X[10]	X[11]	X[11]	X[11]	X[10]	X	X	X[10]	X[11]	X[11]	X[11]		X[6, 25]
Biochemistry[24]	X[9]	X[10]	X[11]	X[11,16]	X[11,16]	X[10]	X[16]	X[16]	X[10]	X[11]	X[11]	X[11]		X[6, 25]
Coagulation factors	X[9]	X[10]				X[10]			X[10]	X[11]	X[11]	X[11]		X[6]
Endocrine[12]	X[9]	X[10]				X[10]			X[10]	X[11]	X[11]	X[11]		X[6]
Urinalysis	X[9]	X[10, 22]				X[10]			X[10]	X[11]	X[11]	X[11]		X[6]
Pregnancy test	X[9]	X[10]				X[10]			X[10]	X[11]	X[11]	X[11]		X[6]
Hepatitis B	X[9]									X[11]				
PK/ADA sampling		Refer to Section 9 and Table 1-16 for details of PK/ADA (immunogenicity) samplings												
Tumor tissue, biomarkers		Refer to Table 1-22 for detailed biomarker assessment schedule												

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities).
ADA=anti-drug antibody; AE=adverse event; CT=computed tomography; EC=expansion cohort; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; beta-hCG=beta-human chorionic gonadotropin; iRECIST=immune Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic; PS=performance status; SCCHN=squamous cell carcinoma of the head and neck; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; UNS=unscheduled.

1. If the subject shows PD or confirmed PD (as per iRECIST), starts new anti-cancer treatment, or withdraws from treatment due to another reason, the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of trial treatment. If the subject initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment (see Section 8.4).
2. Survival follow-up may be performed as telephone, email, or on-site visit.
3. Visit window (±3d) applies to C2D1-C4D1 only.
4. Non-serious AEs and SAEs must be reported from first GEN1046 dose until 60 days after last dose of trial treatment (Section 10.2.1).
5. Full complete physical exam at screening. A targeted physical exam should be performed at Day 1 of each cycle as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator.
6. At investigator's discretion, only if clinically indicated.
7. Temperature, blood pressure and heart rate according to Section 9.4 and Table 1-17 of the protocol on GEN1046 administration days. On days when GEN1046 is not administered, vital signs only need to be obtained once any time during the visit.
8. Suspected trial treatment related SAEs only.
9. All central and local labs at the screening visit must be obtained within 7 days of C1D1 (with the exception of hepatitis B sample, which may be obtained earlier). Hematology, chemistry, endocrine, serum (beta-hCG) pregnancy, and hepatitis B will be performed centrally. Coagulation factors and urinalysis will be performed locally.
10. Local and central laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before for Cycle 2 and beyond. Every effort should be made to obtain local and central labs on the same day. Hematology, chemistry, and endocrine labs should be obtained centrally. Hematology, chemistry, coagulation factors, urine pregnancy, and urinalysis should be performed locally.
11. Central labs should be obtained for hematology and biochemistry on Day 3, Day 8, Day 15 (of relevant cycles), treatment discontinuation and the 30 day and 60-day safety follow-

up visits. Hepatitis B should also be obtained centrally at the treatment discontinuation visit. Coagulation factors, urine pregnancy, and urinalysis should always be performed locally.

12. TSH, T3, and T4 will only be measured at screening, C2D1 (or up to 3 days before C2D1), on Day 1 of every even cycle thereafter (or up to 3 days before the respective Day 1), and at discontinuation.
13. Informed consent may be obtained prior to the screening period. However, C1D1 should be performed within 35 days after informed consent has been obtained.
14. Subjects who experience a delay in the administration of trial treatment should return to the clinic within 3 weeks (±3 days) and an unscheduled visit should be performed. Unscheduled visit assessments should be performed at the investigator's discretion.
15. The Day 3 visit is required only for Cycles 1 and 2.
16. Only for subjects receiving nab-paclitaxel.
17. All subjects will have imaging of brain, thorax, abdomen, and pelvis during screening. Head and neck imaging is always required for subjects with SCCHN. Imaging of the pelvis is not required for subjects with SCCHN but is strongly recommended. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial.
18. On-trial imaging will be performed 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 (unless the investigator elects to continue treatment and follow iRECIST), 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 disease progression, then a subsequent imaging assessment should be performed within 4-7 weeks to confirm progression. Refer to Section 9.2.2 for iRECIST imaging and treatment guidelines.
19. Only Cycle 5 Day 1.
20. On infusion days, ECG before GEN1046 infusion and at the end of GEN1046 infusion + 2 hours (±15 minutes).
21. ECG must be obtained at Cycles 1-3, Cycle 5, Cycle 7, and every 4 cycles thereafter.
22. Urinalysis only on C2D1.
23. CCI [redacted]
24. CCI [redacted]
25. CCI [redacted]

Table 1-12 PK and ADA Sampling in Expansion Cohorts EC1-EC7 and EC9 (Docetaxel Combination)

Treatment Cycle (C)	Screening	Cycle 1-Cycle 2	Cycle 3-Cycle X	Treatment Discontinuation	SFU1	SFU2	UNS
Day (d)	**≤21 days prior to Visit C1 (1d)**	**1d**	**1d[a]**	**-**	**30 days after last dose**	**60 days after last dose**	**-**
PK sampling							
Before GEN1046 infusion (on infusion days)		X	X	X	X	X	X[b]
End of GEN1046 infusion + 2 hours (±15 minutes)		X	X				
ADA sampling							
Before GEN1046 infusion (on infusion days)		X	X		X	X	X

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and PK and ADA sample collection will stop.
ADA=anti-drug antibody; EC=expansion cohort; PK=pharmacokinetic; SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.
[a] PK and ADA must be obtained Cycle 3, Cycle 5, Cycle 7, and every 4 cycles thereafter (ie, Cycles 3, 5, 7, 11, 15, etc).
[b] Optional.

Table 1-13 PK and ADA Sampling in Expansion Cohorts EC8 and EC10, NSCLC Activation/Maintenance Dosing

Treatment Cycle (C)	Cycle 1-Cycle 2 (1Q3W)	Cycle 3 (1Q6W)				Cycle 4 (1Q6W)		Cycle 5-Cycle X (1Q6W)	Treatment Discontinuation	SFU1	SFU2	UNS
Day (d)	**1d**	**1d**	**8d**	**22d**	**36d**	**1d**	**22d**	**Day 1**	**-**	**30 days after last dose**	**60 days after last dose**	**-**
PK sampling												
PK sample[a] (Before GEN1046 infusion on infusion days)	X	X	X	X	X	X	X	X[b]	X	X	X	X[c]
PK sample End of GEN1046 infusion + 2 hours (±15 minutes)	X	X				X		X[b]				
ADA sampling												
Before GEN1046 infusion (on infusion days)	X	X				X		X[b]		X	X	X

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and PK and ADA sample collection will stop.
1Q3W=1 dose every 3 weeks; 1Q6W=1 dose every 6 weeks; ADA=anti-drug antibody; EC=expansion cohort; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.
a. PK sample must be collected before GEN1046 infusion on dosing days.
b. PK and ADA must be collected on Cycle 5, Cycle 6, and every 2 cycles thereafter (ie, Cycles 5, 6, 8, 10, 12 etc).
c. Optional.

Table 1-14 GEN1046 PK and ADA Sampling in Expansion Cohort EC11A NSCLC GEN1046 in Combination with Pembrolizumab with 1Q3W Dosing

Treatment Cycle (C)	**Cycle 1-Cycle 4**		**Cycle 5-Cycle X**	**Treatment Discontinuation**	**SFU1**	**SFU2**	**UNS**
Day (d)	**1d**	**8d**	**1d[b]**	**-**	**30 days after last dose**	**60 days after last dose**	**-**
PK sampling							
PK sample[a] (Before GEN1046 infusion on infusion days)	X	X	X	X	X	X	X[c]
PK sample End of GEN1046 infusion + 2 hours (±15 minutes)	X		X				
ADA sampling							
Before GEN1046 infusion (on infusion days)	X		X		X	X	X

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and PK and ADA sample collection will stop.
1Q3W= 1 dose every 3 weeks; ADA=anti-drug antibody; EC=expansion cohort; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.
a. PK sample must be collected before GEN1046 infusion on dosing days.
b. PK and ADA must be obtained - Cycle 5, Cycle 7, and every 4 cycles thereafter (ie, Cycles 5, 7, 11, 15, etc).
c. Optional.

Table 1-15 GEN1046 PK and ADA Sampling in Expansion Cohort EC11B NSCLC GEN1046 in Combination with Pembrolizumab with 1Q6W Dosing

Treatment Cycle (C)	Cycle 1			Cycle 2	Cycle 3			Cycle 4-Cycle X	Treatment Discontinuation	SFU1	SFU2	UNS
Day (d)	**1d**	**8d**	**22d**	**1d**	**1d**	**8d**	**22d**	**Day 1**	**-**	**30 days after last dose**	**60 days after last dose**	**-**
PK sampling												
PK sample[a] (Before GEN1046 infusion on infusion days)	X	X	X	X	X	X	X	X[b]	X	X	X	X[c]
PK sample End of GEN1046 infusion + 2 hours (±15 minutes)	X			X	X			X[b]				
ADA sampling												
Before GEN1046 infusion (on infusion days)	X			X	X			X[b]		X	X	X

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and PK and ADA sample collection will stop.
1Q6W=1 dose every 6 weeks; ADA=anti-drug antibody; EC=expansion cohort; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.
a. PK sample must be collected before GEN1046 infusion on dosing days.
b. PK and ADA must be collected on Cycle 4, Cycle 5, and every 2 cycles thereafter (ie, Cycles 4, 5, 7, 9, 11 etc).
c. Optional.

Table 1-16 GEN1046 PK and ADA Sampling in Safety Run-in and Expansion Cohorts EC12 and EC13 (GEN1046 in Combination with Pembrolizumab and Platinum-based Chemotherapy Doublets)

Treatment Cycle (C)	Main Treatment Phase (Cycles 1-4)			CCI [redacted] (Cycle 5-Cycle X)	Treatment Discontinuation	SFU1	SFU2	UNS
Day (d)	**1d**	**8d**	**15d**	**Day 1**	-	**30 days after last dose**	**60 days after last dose**	-
PK Sampling								
PK sample[a] Before GEN1046 infusion (on infusion days)	X	X	X	X[b]	X	X	X	X[c]
PK sample End of GEN1046 infusion + 2 hours (±15 minutes)	X			X[b]				
ADA Sampling								
ADA sample Before GEN1046 infusion (on infusion days)	X			X[b]		X	X	X

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and PK and ADA sample collection will stop.
ADA=anti-drug antibody; EC=expansion cohort; NSCLC=non-small cell lung cancer; PK=pharmacokinetic; SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.
a. PK sample must be collected before GEN1046 infusion on dosing days.
b. PK and ADA must be collected on Cycle 5, and every 2 cycles thereafter (ie, Cycles 5, 7, 9, 11, 13, 15, etc.).
c. Optional.

Table 1-17 Vital Signs During Expansion (All Cohorts)

Pre-GEN1046 infusion (up to 30 min before infusion)
At the end of GEN1046 infusion (±10 min)*
1 hour after end of GEN1046 infusion (±10 min)
2 hours after end of GEN1046 infusion (±15 min)

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities).
* If infusion lasts for more than 60 minutes, vital signs should be assessed every 30 minutes (±5 minutes) for the remaining duration of infusion.

1.3.3 Biomarker Assessments – Dose Escalation and Expansion

The following tables list all of the biomarker assessments in dose escalation and expansion and indicate with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

- Table 1-18 Biomarker Table – Dose Escalation (All Cohorts), and Expansion Cohorts EC1-EC7 and EC9 (Docetaxel Combination)
- Table 1-19 Biomarker Table – Expansion Cohorts EC8 and EC10, NSCLC Activation/Maintenance Dosing
- Table 1-20 Biomarker Table – Expansion Cohort EC11A (1Q3W) (Pembrolizumab Combination)
- Table 1-21 Biomarker Table – Expansion Cohort EC11B (1Q6W) (Pembrolizumab Combination)
- Table 1-22 Biomarker Table – Expansion Cohorts EC12 and EC13 (GEN1046 in Combination with Pembrolizumab and Platinum-based Chemotherapy Doublets)

Table 1-18 Biomarker Table – Dose Escalation (All Cohorts), and Expansion Cohorts EC1-EC7 and EC9 (Docetaxel Combination)

Treatment Cycle	**Screening**	**Cycle 1-Cycle 2**					**Cycle 3-Cycle X**		**Treatment Discontinuation**	**Unscheduled**
Day (d)	**≤21 days prior to Visit C1 (1d)**	**1d**	**2d**	**3d**	**8d**	**15d**	**1d**	**8d**	**-**	**-**
Visit window		**±3d[2,7]**	**-**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**-**	**-**
Dose Escalation and Dose Expansion										
Tumor biopsy		X[1]							X[1]	X[1]
Cytokines		X[2]	X	X	X		X	X[2]	X	X[2,8]
Immune phenotyping		X	X	X	X	X	X		X	X[3]
TMB (whole blood)		X[5]								
Dose Expansion Only										
Tumor biopsy	X[1]				X[1]				X[1]	X[1]
TCR profiling[4] (whole blood)		X					X[4]		X	
ctDNA (whole blood)	CCI									
Gene expression profiling (whole blood)		X[6]		X	X					
Immune phenotyping of PBMCs (whole blood)		X[6]					X[6]		X	

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and biomarker sample collection will stop.

C1D1=Cycle 1 Day 1; CRS=cytokine release syndrome; ctDNA=circulating tumor-derived DNA; EC=expansion cohort; FFPE=formalin fixed paraffin embedded; irAE=immune-related adverse event; PBMC=peripheral blood mononuclear cells; TCR=T-cell receptor; TMB=tumor mutational burden.

1 In dose escalation, all subjects must provide an FFPE tumor tissue sample from a fresh tumor biopsy or archival tissue (aspirates are not acceptable) collected before C1D1, preferably derived from advanced stage disease.
In expansion, all subjects must provide a mandatory fresh core-needle biopsy which contains tumor tissue and is taken after failure/stop of last prior treatment and have an on-treatment fresh FFPE tumor biopsy collected. The following samples are not acceptable for this trial: fine needle aspirates, cell blocks, cell pellets, clots, bone marrow or decalcified bone tissue, and any cytological specimens (smears, brushings, washings, lavages, and effusions). Fresh on-treatment biopsies should be collected in Cycle 2 (any time between C2D8 and C2D15 [both inclusive, ie, after 2 doses of GEN1046]) and at disease progression (preferably from a new lesion, if any) or treatment discontinuation where it is considered feasible without a risk of complications for the subject. Furthermore, the latest archival tumor tissue sample should be collected, if available. Details to the preparation of slides and number of slides to be prepared will be described in the lab manual. In case it is not feasible to meet the required criteria for fresh tumor biopsy in escalation or expansion, the sponsor medical monitor's approval for enrollment is needed. If deemed necessary by the investigator, the subject may be called in for an unscheduled visit during dose escalation and dose expansion; optional tumor biopsies may be collected if subjects have unscheduled biopsies or tumor tissue resection during the course of the trial.

2 In dose escalation, cytokine samples on C1D1 and C2D1 will be taken at baseline (pre-dose), 2 hours (±15 minutes) post-infusion, 4-6 hours (±15 minutes) post-infusion, 24 hours (±2 hours), and 48 hours (±2 hours) after end of infusion (however, if it is not possible to take the 48 hour samples 2 days after infusion due to site or subject operational issues, it is acceptable to take the C1D3/C2D3 cytokine sample within the time window [+2 days] as indicated in the table) and pre-dose for Cycle 3 and beyond. If an adverse event of CRS is suspected, cytokines should be obtained at an unscheduled visit to confirm diagnosis.
In expansion, cytokine samples on C1D1 and C2D1 will be taken at baseline (pre-dose), 4-6 hours (±15 minutes) post-infusion, and 24 hours (±2 hours) after end of infusion and pre-dose for Cycle 3 and beyond. Also, in expansion during Cycle 3 and Cycle 4 only, a Day 8 sample will be collected. If an adverse event of CRS is suspected, cytokines should be obtained at an unscheduled visit to confirm diagnosis.
3 Immune phenotyping samples are requested at the time of disease progression or treatment discontinuation.
4 TCR profiling will be done in the expansion cohorts only, and samples will be taken at baseline and at C3D1, and at the time of disease progression or treatment discontinuation.
5 To be taken only once at C1D1.
6 Collected prior to infusion.
7 Visit window (+3d) applies to C2D1 only.
8 CCI [redacted]

Table 1-19 Biomarker Table – Expansion Cohorts EC8 and EC10, NSCLC Activation/Maintenance Dosing

Treatment Cycle	Screening	Cycle 1-Cycle 2 1Q3W			Cycle 3 1Q6W			Cycle 4- Cycle X 1Q6W		Treatment Discontinuation[7]	Unscheduled
Day (d)	**≤35 days prior to Visit C1 (1d)**	**1d**	**8d**	**15d**	**1d**	**8d**	**22d**	**1d**	**22d**	**-**	**-**
Visit window		**+3d**	**±1d**	**±1d**	**±3d**	**±1d**	**±2d**	**±3d**	**±2d**	**-**	**-**
Tumor tissue[3]	X[1,2]		X[4]						X[4]	X[4]	X[9]
Cytokines		X[5]	X		X[5]	X	X	X[5]	X	X	X[6]
Immune phenotyping		X[5]	X	X	X[5]	X	X	X[5]	X	X	X
TCR profiling[8] (whole blood)		X[5]			X[5]			X[5] (C5 only)		X	
TMB (whole blood)		X[5] (C1 only)									
ctDNA (whole blood)	CCI [redacted]										
Immune phenotyping of PBMCs (whole blood)		X[5]			X[5]		X	X[5]	X	X	

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and biomarker sample collection will stop.

1Q3W=once (1 dose) every 3 weeks; 1Q6W=once (1 dose) every 6 weeks; C1D1=Cycle 1 Day 1; ctDNA=circulating tumor-derived DNA; EC=expansion cohort; FFPE=formalin fixed paraffin embedded; irAE=immune-related adverse event; NSCLC=non-small cell lung cancer; PBMC=peripheral blood mononuclear cells; PD-L1=programmed death-ligand 1; TCR=T cell receptor; TMB=tumor mutational burden.

1 In EC8, all subjects must provide an FFPE tumor sample that is of sufficient histological quality and has preserved tissue architecture (ie, core-needle biopsies, histological punctures, biopsies performed with mini-forceps, resections) and must originate from the metastatic stage of the cancer. The tumor tissue should ideally be from the same block of tumor used for local PD-L1 testing, if applicable. If prospective PD-L1 testing at sponsor-designated central laboratory is needed for eligibility in case local testing is not feasible or does not meet the specified criteria CCI [redacted], the tumor sample should be submitted to the central laboratory as soon as possible after informed consent has been obtained in order to have the PD-L1 expression result available prior to C1D1. NOTE: C1D1 must be performed no later than 35 days after informed consent has been obtained.

2 In EC10, all subjects must provide a fresh FFPE tumor sample which is obtained by core-needle biopsy and is taken after failure/stop of last prior treatment. The tumor sample should be submitted to the central laboratory as soon as possible after informed consent has been obtained in order to have the PD-L1 expression result available prior to C1D1. NOTE: C1D1 must be performed no later than 35 days after informed consent has been obtained. Furthermore, the latest archival tumor tissue sample should be collected if available.

3 The following samples are not acceptable for EC8 and EC10: fine needle aspirates, cell blocks, cell pellets, clots, bone marrow or decalcified bone tissue, and any cytological specimens (smears, brushings, washings, lavages, and effusions).

4 Subjects in EC8 and EC10 must also have on-treatment tumor biopsies collected in Cycle 2 (any time between C2D8 and C2D15 [both inclusive, ie, after 2 doses of GEN1046]), Cycle 4 (C4D22 ±2 days), and at disease progression (preferably from new lesion, if any) or treatment discontinuation where it is considered feasible without a risk of complications for the subject.

5 Collected prior to infusion of GEN1046.

6 CCI [redacted]

7 Biomarker samples are requested at the time of disease progression or treatment discontinuation.
8 In EC8 and EC10, samples for TCR profiling will be taken at baseline (C1D1), C2D1, C3D1, C5D1, and at the time of disease progression or treatment discontinuation.
9 If deemed necessary by the investigator, the subject may be called in for an unscheduled visit and optional tumor biopsies may be collected if subjects have unscheduled biopsies or tumor tissue resection during the course of the trial.

Table 1-20 Biomarker Table – Expansion Cohort EC11A (1Q3W) (Pembrolizumab Combination)

Treatment Cycle	Screening	Cycle 1-2			Cycle 3-4		Cycle 5 Onward	Treatment Discontinuation	Unscheduled Visit
Day (d)	**≤35d prior to C1D1**	**1d**	**3d**	**8d**	**1d**	**8d**	**1d**		
Visit window		**+3d**	**+1d**	**±1d**	**±3d**	**±1d**	**±3d**		
Tumor tissue	X[1]			X[2]				X[2]	X[3]
Cytokines		X[4]	X	X	X[4]	X		X	X[5]
Immune phenotyping		X[4]	X	X	X[4]	X		X	X
Immune phenotyping of PBMCs (whole blood)		X[4]			X[4]		X[4]	X	
ctDNA (whole blood)	CCI [redacted]								
TCR profiling (whole blood)		X[4]			X[4]			X	
TMB (whole blood)		X[4] (C1 only)							

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and biomarker sample collection will stop.

1Q3W=1 dose every 3 weeks; C1D1=Cycle 1 Day 1; ctDNA=circulating tumor-derived DNA; irAE=immune-related adverse event; PBMCs=peripheral blood mononuclear cells; PD-L1=programmed death-ligand 1; TCR=T-cell receptor; TMB=tumor mutational burden.

1 In EC11A, all subjects should provide an FFPE tumor sample that is of sufficient histological quality and has preserved tissue architecture (ie, core-needle biopsies, histological punctures, biopsies performed with mini-forceps, resections) and must originate from the metastatic stage of the cancer. The tumor tissue should ideally be from the same block of tumor used for local PD-L1 testing, if applicable. The following samples are not acceptable for this trial: fine needle aspirates, cell blocks, cell pellets, clots, bone marrow or decalcified bone tissue, and any cytological specimens (smears, brushings, washings, lavages, and effusions). If prospective PD-L1 testing at sponsor-designated central laboratory is needed for eligibility in case local testing is not feasible or does not meet the specified criteria CCI [redacted], the tumor sample should be submitted to the central laboratory as soon as possible after informed consent has been obtained in order to have the PD-L1 expression result available prior to C1D1. NOTE: C1D1 must be performed no later than 35 days after informed consent has been obtained.

2 Subjects should also have on-treatment tumor biopsies performed in Cycle 2 (any time between C2D8 and C2D15 [both inclusive, ie, after 2 doses of GEN1046]) and at disease progression (preferably from a newly diagnosed lesion, if any) or treatment discontinuation if clinically feasible.

3 If deemed necessary by the investigator, tumor biopsies may also be collected if subjects have unscheduled biopsies or tumor tissue resection during the course of the trial.

4 Collected prior to infusion of GEN1046.

5 CCI [redacted]

Table 1-21 Biomarker Table – Expansion Cohort EC11B (1Q6W) (Pembrolizumab Combination)

Treatment Cycle	Screening	Cycle 1-2				Cycle 3-4			Cycle 5 Onward	Treatment Discontinuation	Unscheduled Visit
Day (d)	**≤35d prior to C1D1**	**1d**	**3d**	**8d**	**22d**	**1d**	**8d**	**22d**	**1d**		
Visit window		**+3d**	**+1d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**		
Tumor tissue	X[1]			X[2]						X[2]	X[3]
Cytokines		X[4]	X	X	X	X[4]	X	X		X	X[5]
Immune phenotyping		X[4]	X	X	X	X[4]	X	X		X	X
Immune phenotyping of PBMCs (whole blood)		X[4]			X	X[4]		X	X[4]	X	
ctDNA (whole blood)	CCI [redacted]										
TCR profiling (whole blood)		X[4]			X	X[4]				X	
TMB (whole blood)		X[4] (C1 only)									

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and biomarker sample collection will stop.

1Q6W=1 dose every 6 weeks; C1D1=Cycle 1 Day 1; C2D1=Cycle 2 Day 1; ctDNA=circulating tumor-derived DNA; irAE=immune-related adverse event; PBMCs=peripheral blood mononuclear cells; PD-L1=programmed death-ligand 1; TCR=T-cell receptor; TMB=tumor mutational burden.

1 In EC11B, all subjects should provide an FFPE tumor sample that is of sufficient histological quality and has preserved tissue architecture (ie, core-needle biopsies, histological punctures, biopsies performed with mini-forceps, resections) and must originate from the metastatic stage of the cancer. This tumor tissue should ideally be from the same block of tumor used for local PD-L1 testing, if applicable. The following samples are not acceptable for this trial: fine needle aspirates, cell blocks, cell pellets, clots, bone marrow or decalcified bone tissue, and any cytological specimens (smears, brushings, washings, lavages, and effusions). If prospective PD-L1 testing at sponsor-designated central laboratory is needed for eligibility in case local testing is not feasible or does not meet the specified criteria CCI [redacted], the tumor sample should be submitted to the central laboratory as soon as possible after informed consent has been obtained in order to have the PD-L1 expression result available prior to C1D1. NOTE: C1D1 must be performed no later than 35 days after informed consent has been obtained.
2 Subjects should also have on-treatment tumor biopsies performed in Cycle 2 (any time between C2D8 and C2D15 [both inclusive, ie, after 2 doses of GEN1046]) and at disease progression (preferably from a newly diagnosed lesion, if any) or treatment discontinuation, if clinically feasible.
3 If deemed necessary by the investigator, tumor biopsies may also be collected if subjects have unscheduled biopsies or tumor tissue resection during the course of the trial.
4 Collected prior to infusion of GEN1046.
5 CCI [redacted]

Table 1-22 Biomarker Table – Expansion Cohorts EC12 and EC13 (GEN1046 in Combination with Pembrolizumab and Platinum-based Chemotherapy Doublets)

Treatment Cycle (C)	Screening	Main Treatment Phase					CCI			Treatment Discontinuation	Unscheduled Visit
		Cycle 1			Cycles 2-4		Cycles 5-6		Cycle 7 onward		
Day (d)	**≤35d prior to C1D1**	**1d**	**3d**	**8d**	**1d**	**8d**	**1d**	**8d**	**1d**	**-**	**-**
Visit window			**+1d**	**±1d**	**±3d**	**±1d**	**±3d**		**±3d**	**-**	**-**
Tumor tissue	X[1]					X[2]				X[2]	X[3]
Cytokines		X[4]	X	X	X[4]	X	X[4]	X		X	X[5]
Immune phenotyping		X[4]	X	X	X[4]	X	X[4]	X		X	X
Immune phenotyping of PBMCs (whole blood)		X[4]			X[4]		X[4]		X[4]	X	
ctDNA (whole blood)	CCI										
TCR profiling (whole blood)		X[4]			X[4]					X	
TMB (whole blood)		X[4]									

NOTE: After the primary analysis cutoff date (Section 11.12.2), all ongoing subjects will transition to Table 1-23 (Post-Primary Analysis Schedule of Activities) and biomarker sample collection will stop.
C1D1=Cycle 1 Day 1; C2D1=Cycle 2 Day 1; ctDNA=circulating tumor-derived DNA; EC=expansion cohort; FFPE=formalin fixed paraffin embedded; irAE=immune-related adverse event; PBMCs=peripheral blood mononuclear cells; PD-L1=programmed death-ligand 1; TCR=T-cell receptor; TMB=tumor mutational burden.

1 In EC12 and EC13, all subjects must provide an FFPE tumor sample that is of sufficient histological quality and has preserved tissue architecture (ie, core-needle biopsies, histological punctures, biopsies performed with mini-forceps, resections) and must originate from the metastatic stage of the cancer. The tumor tissue should ideally be from the same block of tumor used for local PD-L1 testing. The following samples are not acceptable for this trial: fine needle aspirates, cell blocks, cell pellets, clots, bone marrow or decalcified bone tissue, and any cytological specimens (smears, brushings, washings, lavages, and effusions).
2 Subjects should also have on-treatment tumor biopsies performed in Cycle 2 (any time between C2D8 and C2D15 [both inclusive, ie, after 2 doses of GEN1046]) and at disease progression (preferably from a newly diagnosed lesion, if any) or treatment discontinuation, if clinically feasible.
3 If deemed necessary by the investigator, tumor biopsies may also be collected if subjects have unscheduled biopsies or tumor tissue resection during the course of the trial.
4 Collected prior to infusion of GEN1046.
5 CCI

1.3.4 Post-Primary Analysis Schedule of Activities – All Subjects

Table 1-23 Post-Primary Analysis Schedule of Activities – All Subjects

Visit		**Cycle 5-Cycle X** CCI [redacted]		**Treatment discontinuation[2]**	**Safety follow-up 1[3]**	**Safety follow-up 2[3]**	**Survival follow-up[4]**	**UNS[5]**
Day/Week		**1d**	**22d** CCI [redacted]	**-**	**30 days after last dose**	**60 days after last dose**	**Q12W after last dose**	
Visit window		**±3d**	**±3d**	**-**	**+5d**	**±7d**	**±14d**	
GENERAL AND SAFETY ASSESSMENTS								
Body weight		X		X				
Physical examination		X	X	X	X			X
Vital signs[6]		X	X	X	X			X
ECG								X
CT/MRI scan		Refer to Section 9.2 for details on imaging assessments[7]						
ECOG performance status		X	X	X	X			X
Adverse events[8]		X	X	X	X	X	X[9]	X
Concomitant medication		X	X	X	X	X		X
End of treatment				X				
New anti-cancer treatment				X	X	X	X	
Survival follow-up							X	
LOCAL LABORATORY ASSESSMENTS								
Hematology		X[10]	X	X	X	X		X
Biochemistry[11]		X[10]	X	X	X	X		X
Coagulation factors		X[10]		X	X	X		X
Endocrine[12]		X[10]		X	X	X		X
Urinalysis		X[10]		X	X	X		X
Pregnancy test		X[10]		X	X	X		X
Hepatitis B				X				X
TRIAL TREATMENT (For Active Subjects Only)								
Escalation, EC4, EC11A, EC12, EC13	GEN1046 Q3W	X						
EC8, EC10, EC11B	GEN1046 Q6W	X						
EC11A, EC12, EC13	Pembrolizumab 1Q3W	X						
EC11B	Pembrolizumab 1Q6W	X						
EC12	Pemetrexed 1Q3W	X						

AE=adverse event; CT=computed tomography; D/d = day; EC = expansion cohort; ECG=electrocardiogram; ECOG= Eastern Cooperative Oncology Group; irAE=immune-related adverse event; iRECIST=immune Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; PD=progressive disease; 1Q3W=every 3 weeks; 1Q6W=every 6 weeks; Q12W=every 12 weeks; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; UNS=unscheduled

1 1Q3W (21-day cycle) for subjects in the following cohorts: dose escalation, EC4, EC11A, EC12, EC13
1Q6W (42-day cycle) for subjects in the following cohorts: EC8, EC10, EC11B

2 If the subject shows PD or confirmed PD (as per iRECIST), starts new anti-cancer treatment, or withdraws from treatment due to another reason, the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of trial treatment.

3 If the subject initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment (see Section 8.4).

4 Survival follow-up visits may be performed as telephone, email, or visit.

5 Assessments at an unscheduled visit should only be performed as clinically indicated.

6 Temperature, blood pressure, and heart rate according to Section 9.4. Vital signs should be performed pre-GEN1046 infusion (up to 30 minutes before infusion), at the end of GEN1046 infusion (±10 minutes), and 1 hour (±10 minutes) and 2 hours after end of GEN1046 infusion (±15 minutes). If infusion lasts for more than 60 minutes, vital signs should be assessed every 30 minutes (±5 minutes) for the remaining duration of infusion.

7 On-trial imaging will be performed 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 (unless the investigator elects to continue treatment and follow iRECIST), 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 disease progression, then a subsequent imaging assessment should be performed within 4-7 weeks to confirm progression. Refer to Section 9.2.2 for iRECIST imaging and treatment guidelines.

8 Non-serious AEs and SAEs must be reported from first GEN1046 dose until 60 days after last dose of trial treatment (Section 10.2.1).

9 Suspected trial treatment-related SAEs only.

10 Local laboratory samples should be obtained up to 3 days before D1 for each cycle.

11 CCI

12 TSH, T3, and T4 will only be measured on Day 1 of every even cycle (or up to 3 days before the respective Day 1).

2 INTRODUCTION

2.1 Background

This is an open-label, multicenter, phase 1/2a safety trial of GEN1046 (DuoBody®PD-L1×4-1BB). The trial consists of 2 parts; a first-in-human (FIH) dose escalation (phase 1) and an expansion (phase 2a). The dose escalation evaluates GEN1046 in subjects with solid malignant tumors to determine the maximum tolerated dose (MTD) or maximum administered dose and/or the recommended phase 2 dose (RP2D). The expansion further evaluates the safety, tolerability, PK, and anti-tumor activity of the selected dose(s) in select solid tumors.

The clinical success of immune checkpoint inhibitor (CPI) antibodies has demonstrated that therapeutic treatments that are able to (re-)activate anti-tumor immunity show great promise for the treatment of cancer. Similarly, therapeutic agents that boost anti-tumor immunity by direct activation of immunostimulatory molecules may provide clinical benefit. GEN1046 is a PD-L1×4-1BB bispecific antibody that induces conditional activation of T cells through 4-1BB stimulation, which is dependent on simultaneous binding to programmed death-ligand 1 (PD-L1). The fragment crystallizable (Fc) domain of GEN1046 was engineered to silence interactions with the Fc γ receptor (FcγR) and the complement factor C1q. Thereby, GEN1046-mediated stimulation of 4-1BB signaling in activated T cells is strictly dependent on simultaneous binding of the PD-L1-binding arm. In addition, the PD-L1-specific arm of GEN1046 functions as a classical immune CPI by blocking the programmed cell death protein 1 (PD-1)/PD-L1 axis, also in the absence of 4-1BB binding. The hypothesis is that by simultaneous binding of PD-L1 on tumor cells or antigen presenting cells and 4-1BB on tumor-specific T cells, GEN1046 will induce efficacious T-cell activation in the tumor or in tumor-draining lymph nodes, thereby enhancing anti-tumor immunity. GEN1046 (BNT311) is being jointly developed by Genmab and BioNTech for the treatment of solid malignant tumors.

2.1.1 Overview of Disease

2.1.1.1 Lung Cancer – NSCLC

Lung cancer is the second most common malignancy with an estimated age-standardized incidence rate of 22.4 per 100,000 and a leading cause of cancer death for both men and women (Kantar, 2021). NSCLC includes 2 major types: non-squamous and squamous cell carcinoma (Howlader et al., 2021). Worldwide, approximately 2,206,771 new cases of lung cancer and 1,796,144 deaths were estimated in 2020 (GLOBOCAN, 2020). Non-small cell lung cancer (NSCLC) accounts for 85% to 90% of all cases, with a 5-year survival rate of approximately 18% across all stages of the disease, and only 3.5% for metastatic disease (Jemal et al., 2011; Kantar, 2021; SEER, 2018). In the first-line (1L) setting, treatment typically consists of platinum-based chemotherapy in combination with immunotherapy, or a targeted therapy, depending on molecular and biomarker analysis and the histology of the tumor (NCCN, 2021). More recently, the advent of PD-1 and PD-L1 inhibitors have improved outcomes for patients without driver mutations (approximately 62% of the non-squamous population and 77% of the squamous population (Kantar, 2021)). More treatment alternatives are needed for patients whose tumors do not harbor certain oncogenic mutations or do not express the biomarkers for CPI options. Novel combinations with complementary approaches to enhance response may further address the unmet need in this population. For patients in the second-line (2L) setting, standard of care (SOC) is limited to platinum-based chemotherapy, a CPI monotherapy, or docetaxel with

or without ramucirumab depending on the previous therapy received. For patients in the third-line setting, chemotherapy monotherapy is the standard. Novel therapies are needed to limit toxicity and potentially enhance efficacy in this population (NCCN, 2021).

2.1.1.2 Urothelial Cancer – UC

In the United States (US), 76,900 new urinary bladder cancer cases and 16,390 deaths were estimated in 2016. Five-year relative survival rates in the US are 34% for patients with regional disease at diagnosis and only 5% for patients with distant disease at diagnosis (rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2005-2011, all followed through 2012).

Treatment for advanced bladder cancer has historically included gemcitabine or taxane-based chemotherapy regimens besides dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin and chemo-radiotherapy (NCCN, 2018a). The paucity of approved targeted agents for the treatment of bladder cancer has shifted with the recent approvals of several CPIs. The US Food and Drug Administration (FDA) has approved the PD-L1 inhibitors atezolizumab, durvalumab, and avelumab, as well as the PD-1 inhibitors nivolumab and pembrolizumab for the treatment of locally advanced or metastatic urothelial carcinoma (UC) that has progressed during or after platinum-based chemotherapy or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy, regardless of PD-L1 expression levels (Ribas and Wolchok, 2018).

The largest study to evaluate PD-1 or PD-L1 inhibitors as 2L therapy for patients with UC who previously experienced progression on a platinum-based therapy is the KEYNOTE-045 trial. This open-label, randomized, phase 3 trial compared pembrolizumab to chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients. Median overall survival (OS) for patients treated with pembrolizumab was 10.3 months vs 7.4 months for those who received chemotherapy. In addition, fewer grades 3, 4, or 5 treatment-related adverse events (TRAEs) occurred in the pembrolizumab-treated patients compared to those treated with chemotherapy (15.0% vs 49.4%) (Bellmunt et al., 2017). Similar outcomes were reported in other trials evaluating PD-1 or PD-L1 targeted agents in patients with metastatic disease post-platinum treatment; response rates observed with atezolizumab, nivolumab, durvalumab, and avelumab ranged from 15.0% to 19.6% (NCCN, 2018a).

Performance status is also an important consideration in the selection of a regimen for UC (NCCN, 2018a). Non-cisplatin-containing regimens may be considered in patients who cannot tolerate cisplatin due to renal impairment or other comorbidities. Pembrolizumab and atezolizumab are also approved for 1L treatment in patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy.

Data from a single-arm phase 2 trial evaluating pembrolizumab as 1L therapy in 370 patients with advanced UC who were ineligible for cisplatin-based therapy showed an overall response rate of 24%, with 5% of patients achieving a complete response (CR) (Balar et al., 2017a). Similarly, an objective response rate (ORR) of 23% was observed in a phase 2 study evaluating atezolizumab as a 1L therapy in patients with locally advanced or metastatic UC who were ineligible for cisplatin (Balar et al., 2017b).

UC remains an indication of high unmet medical need especially for patients who have failed therapy with approved SOC regimens. The early success of PD-1 and PD-L1 inhibitors as

monotherapy treatment for advanced or metastatic UC to date has yielded promising results. Nevertheless, median survival remains less than 1 year and highlights the importance of improving treatment options in this population.

2.1.1.3 Endometrial Cancer

In the US as well as other developed countries, uterine endometrial cancer was the most common gynecological malignancy, with increasing incidence globally. In the US, there were estimated 60,000 new cases reported and over 10,000 deaths in 2016 (Siegel et al., 2016). Worldwide in 2012, 527,600 women were diagnosed with uterine endometrial cancer (Torre et al., 2015). Several risk factors are associated with the risk of developing endometrial cancer including increased levels of estrogen, early age at menarche, nulliparity, late age at menopause, Lynch syndrome, older age, and tamoxifen use (NCCN, 2018c).

A majority of endometrial cancer cases are identified at an early stage and are treated with surgery with or without radiotherapy or chemotherapy. However, patients with advanced disease have a poorer prognosis with a 5-year survival rate of less than 50% for patients with lymph node metastases and less than 20% for patients with peritoneal or distant metastases (Dowdy, 2014).

Multi-agent chemotherapy is the preferred treatment for metastatic, recurrent, or high-risk disease; however, there is no consensus on a standard regimen. Carboplatin and paclitaxel is increasingly used in the 1L setting for advanced/metastatic or recurrent endometrial cancer. Response rates with carboplatin and paclitaxel range from 40% to 62% with an OS of approximately 13 to 29 months. Results from the GOG 209 phase 3 trial comparing carboplatin and paclitaxel vs cisplatin, doxorubicin, paclitaxel, and filgrastim showed similar outcomes but a favorable tolerability and toxicity profile for the carboplatin and paclitaxel combination (NCCN, 2018c). The addition of bevacizumab to carboplatin and paclitaxel has also been explored and showed improved outcomes in a small subset of patients. In a retrospective analysis of 42 patients who received carboplatin, paclitaxel, and bevacizumab, an ORR of 82.8% was observed however, further studies are needed to confirm improved outcomes with the addition of bevacizumab to standard chemotherapy. Patients who progress on combination therapy or who are unable to tolerate multi-agent chemotherapy may receive single-agent therapy, however, chemotherapeutic options in this setting have produced only modest activity, especially in the 2L setting and beyond. Single agent response rates range from 21% to 36% in the 1L setting and 4% to 27% in the 2L setting (NCCN, 2018c).

Most recently, pembrolizumab has demonstrated anti-tumor activity in patients with locally advanced or metastatic PD-L1+ endometrial cancer who experienced progression on or after standard therapy. Three of 24 (13%) patients achieved a confirmed partial response (PR) and an additional 3 patients achieved stable disease (SD) (Ott et al., 2017). A small subset of patients with deficient mismatch repair (dMMR) endometrial cancer have also shown notable benefit from treatment with PD-1 inhibitors. Among 15 dMMR EC patients who received pembrolizumab, an ORR of 52% (3 CR, 5 PR) was observed with a disease control rate (DCR) or 73% (Le et al., 2017). In 2017, the FDA expanded pembrolizumab approval to include treatment of unresectable or metastatic, microsatellite instability (MSI)-high or dMMR solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options (NCCN, 2018c).

Despite modest improvement in outcomes for patients with endometrial cancer in recent years, the unmet medical need to find new tolerable treatment options remains high.

2.1.1.4 Breast Cancer – TNBC

Breast cancer is the most common cancer in women worldwide with approximately 1.7 million new cases diagnosed in 2012 (Ferlay et al., 2015). Triple-negative breast cancer (TNBC) accounts for about 15% to 20% of breast cancers. TNBC tumors lack the expression of estrogen receptor (ER) and progesterone receptor (PgR), and do not show amplification of the human epidermal growth factor receptor 2 (HER2) gene. A more frequent association of TNBC has been found with African-American women, younger age, higher grade, more advanced stage at diagnosis, and is associated with breast cancer gene (BRCA) mutations (Abramson et al., 2015).

Anthracycline and taxane-based chemotherapy is the treatment of choice for patients with TNBC. Platinum-based chemotherapy has also been incorporated in the neoadjuvant and metastatic settings and despite high response rates with chemotherapy, median OS for women with metastatic TNBC is less than 1 year (Dent et al., 2007). Furthermore, patients with TNBC do not benefit from targeted therapies such as endocrine therapy or trastuzumab and no molecular targets have been identified (Santonja et al., 2018).

A high unmet medical need remains for women with metastatic TNBC, as this disease usually progresses rapidly following 3 to 5 lines of chemotherapy. Considerable interest has been generated by the encouraging results obtained with the immune CPIs pembrolizumab and atezolizumab in heavily pretreated women with advanced stage TNBC. The ORR to these agents remains modest (~18%), but the median duration of response (DoR) had not been reached at the time of publication, indicating sustained responses rarely observed in patients with heavily pretreated TNBC (Piccart and Gingras, 2016).

2.1.1.5 Squamous Cell Carcinoma of the Head and Neck – SCCHN

Squamous cell carcinoma of the head and neck (SCCHN) is a major cause of death with over 600,000 cases diagnosed annually worldwide (Ferlay et al., 2015). In 2018, approximately 64,690 people will develop oral cavity, pharyngeal, or laryngeal cancers in the US and an estimated 13,740 deaths will occur over the same period (NCCN, 2018b). Head and neck cancers can arise in the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands. Tobacco use and alcohol greatly increase the risk of developing head and neck cancer. In addition, human papillomavirus (HPV) infection has a causal association with squamous cancers of the oropharynx (particularly tonsils and base of tongue) and recent evidence suggests that HPV may also be associated with increased risk of squamous cell carcinoma of the larynx (Chen et al., 2017). Patients with locally HPV-positive head and neck cancers have improved outcomes for response to treatment, progression-free survival (PFS), and OS as compared with HPV-negative tumors (Fakhry et al., 2008).

Treatment of head and neck cancers is complex and requires a multidisciplinary approach. The prognosis of patients with recurrent or metastatic SCCHN is generally poor with a median survival of approximately 6 to 12 months depending on patient's performance status and disease-related factors. 1L therapy for fit patients includes cetuximab with cisplatin or carboplatin plus 5-fluorouracil (5-FU). The addition of cetuximab resulted in prolonged survival as compared with platinum and 5-FU alone (10.1 months vs 7.4 months) as well as prolonged median PFS (3.3 months vs 5.6 months) (Vermorken et al., 2008). Single agent chemotherapy is

recommended for patients with poorer performance status. In the past, the most widely used single agents included platinum compounds, taxanes, nab-paclitaxel, methotrexate, fluorouracil, and cetuximab (NCCN, 2018b).

In the US and several other countries, pembrolizumab and nivolumab are approved for patients with progressive disease (PD) after platinum-containing chemotherapy. In one open-label phase 3 trial, 361 patients with recurrent SCCHN who had progressed within 6 months after platinum-based chemotherapy were randomized to nivolumab or standard single agent therapy (methotrexate, docetaxel, or cetuximab). Median OS was 7.5 months in the nivolumab group vs 5.1 months in the group that received standard therapy and the response rate was 13.3% in the nivolumab group vs 5.8% in the standard-therapy group (Ferris et al., 2016). Similar efficacy was reported with pembrolizumab. While data from trials exploring the single agent activity of PD-1 targeted appear encouraging, response rates remain low. Therefore, SCCHN remains an area of high unmet medical need and further opportunity exists to improve outcomes with novel treatment approaches.

2.1.1.6 Cervical Cancer

Cervical cancer poses a significant medical problem worldwide with an estimated incidence of more than 500,000 new cases. In the US, approximately 12,800 new cases and 4210 deaths are estimated to occur in 2017 (American Cancer Society, 2017). In countries that do not have access to cervical cancer screening and prevention programs, cervical cancer is the second most common type of cancer (17.8 per 100,000 women) and cause of death (9.8 per 100,000) among all types of cancer (WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre), 2010).

Cervical cancer is a disease of young women, with a median age of diagnosis of 49 years in the US and even lower in developing countries. While the 5-year survival rate for patients in the US diagnosed with localized disease is 91% (Howlader et al., 2017), the prognosis for patients with advanced disease remains poor. Five-year survival rates for advanced/metastatic disease are less than 35% (stage IIIA cancer ~35%, stage IIIB cancer ~32%, stage IVA cancer ~16%, and stage IVB cancer~15%) (American Cancer Society, 2017).

1L treatment for recurrent or metastatic cervical cancer is comprised of bevacizumab combined with paclitaxel and platinum (cisplatin or carboplatin) or paclitaxel and topotecan. Despite a 48% ORR and a median OS of approximately 18 months, almost all patients relapse after this 1L treatment (Tewari et al., 2014). For 2L therapy, pembrolizumab is approved in the US for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy and whose tumors express PD-L1 as determined by an FDA-approved test. The indication is approved under accelerated approval based on tumor response rate and DoR. The indication was based on data from the phase 2, KEYNOTE-158 single patient cohort trial of patients with recurrent or metastatic cervical cancer. The ORR was 14.3% (95% CI, 7.4-24.1) in 77 PD-L1+ patients with a combined positive score ≥1 previously treated with ≥1 line of chemotherapy in the metastatic setting. The median DoR was not reached (range, 4.1 to 18.6+), and 91% of responders had a response duration of 6 months or longer (Chung et al., 2019). Continued approval is contingent upon verification and description of clinical benefit in the confirmatory trials. No additional approved therapies are available however, patients are often treated with single agent modalities including, but not limited to: pemetrexed, topotecan, docetaxel, nab-paclitaxel, vinorelbine, and in some cases bevacizumab. Response rates with

single agent treatment are very low (range: 0% to 15%) and for this reason, cervical cancer remains a population of very high unmet medical need.

2.1.2 Introduction to Investigational Treatment

GEN1046 is a bispecific antibody that induces conditional activation of T cells through 4-1BB stimulation, which is dependent on simultaneous binding to PD-L1. In addition, the PD-L1-specific arm of GEN1046 functions as a classical immune CPI by blocking the PD-1/PD-L1 axis, also in the absence of 4-1BB binding. GEN1046 is being jointly developed by Genmab and BioNTech for the treatment of solid malignant tumors.

The mechanism of action (MoA) of GEN1046 is distinct from that of chemotherapy or conventional PD-L1- and 4-1BB-targeting immunoglobulin G (IgG) monoclonal antibodies (mAbs). Although the PD-L1-specific arm of GEN1046 functions as a classical CPI by blocking the PD-1/PD-L1 axis also in the absence of 4-1BB binding, the addition of a 4-1BB-stimulating arm further enhances T-cell activation. Conventional 4-1BB-targeting antibodies are typically dependent on direct agonist activity, or agonist activity through FcγR-mediated antibody crosslinking. 4-1BB agonist activity by GEN1046 is conditional; it is dependent on simultaneous binding of GEN1046 to both 4-1BB and PD-L1. Binding of GEN1046 to 4-1BB in absence of PD-L1-expressing cells does not induce agonist activity. The Fc domain of GEN1046 was engineered to silence interactions with FcγR and the complement factor C1q, thereby preventing 4-1BB agonist activity through FcγR-mediated crosslinking of membrane-bound GEN1046 and cytotoxic activity through FcγR-mediated effector functions and complement-mediated cytotoxicity. In conclusion, GEN1046-mediated signaling of 4-1BB on activated T cells is strictly dependent on simultaneous binding of the PD-L1-binding arm.

GEN1046 is generated using Genmab's DuoBody® technology (Labrijn et al., 2013; Labrijn et al., 2014). Structurally, GEN1046 is similar to a conventional IgG1 molecule, with the exception of 4 amino acids in the Fc region that have been altered to allow generation of a stable bispecific molecule and to silence Fc-mediated effector functions. The capacity to bind the neonatal Fc receptor is preserved, providing for the relatively long plasma half-life that is typical for IgG1 molecules.

The unique MoA of GEN1046 supports the notion that GEN1046 is a promising therapeutic agent with potential anti-tumor effect in many different cancer types.

2.1.3 Summary of Nonclinical Studies

A nonclinical data package, consisting of nonclinical pharmacology and toxicology studies in vitro and in vivo, is available for GEN1046.

GEN1046 bound to PD-L1- or 4-1BB-expressing primary human immune cells with EC_{50} values in the high picomolar range as determined by flow cytometry, which was comparable to the affinity (K_D) for recombinant human PD-L1 and 4-1BB protein as determined by biolayer interferometry. In addition, GEN1046 binds to PD-L1-expressing tumor cells and efficiently blocks PD-1/PD-L1 interactions in vitro.

GEN1046 enhanced proliferation of activated T cells in the presence of PD-L1+ cells in vitro, both after polyclonal and antigen-specific activation of T cells. The highest levels of T-cell proliferation were observed upon crosslinking of PD-L1- and 4-1BB-positive cells by GEN1046.

Binding of only the PD-L1 arm enhanced T-cell proliferation to a lesser extent, while binding of the only 4-1BB arm had no effect on T-cell proliferation. EC_{50} values for GEN1046-induced enhancement of $CD8^+$ T-cell proliferation were in the picomolar range. Consistent with the lack of 4-1BB expression on resting T cells, GEN1046 did not induce proliferation in T cells that had not been activated polyclonally or by exposure to their cognate antigen. In these in vitro T-cell proliferation assays, GEN1046 additionally enhanced secretion of pro-inflammatory cytokines. In vivo studies using a mouse cross-reactive surrogate antibody for GEN1046, demonstrated that crosslinking of PD-L1 and 4-1BB with a bispecific antibody enhanced proliferation of antigen-specific adoptively transferred (OT-1) T cells in vivo, after vaccination with the specific antigen (ovalbumin [OVA]).

Immunohistochemistry (IHC) analysis in a small study using frozen human tonsil and placental tissues sections showed that GEN1046, as expected, bound to immune cells (mononuclear cells [tonsil]) and non-immune cells (crypt epithelium [tonsil], trophoblasts [placenta]) with the PD-L1 Fab arm, and to immune cells (mononuclear cells [tonsil]) only with the 4-1BB Fab arm.

The nonclinical safety program with GEN1046 consists of in vitro studies using human cells and tissues (cytokine release assay, hemolytic potential, plasma compatibility, and tissue cross-reactivity), and in vivo studies in cynomolgus monkeys. The cynomolgus monkey was selected as the preferred toxicology species based on in vitro studies demonstrating that this is the only species where GEN1046 binds to both PD-L1 and 4-1BB.

The cytokine release assay was conducted using human whole blood from 30 donors with the purpose of hazard identification relative to potential first-infusion reactions. In this assay, GEN1046 at concentrations ≤10 µg/mL, did not induce notably elevated median levels of any of the screened cytokines (Interleukin [IL]-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor [TNF]α). Based on individual donor responses, a few donors had higher levels of some cytokines (IL-2, IL-6, IL-8, TNFα, interferon [IFN]γ). However, across the 30 donors the median levels were generally low. These results suggest that GEN1046 represents a low risk for first-infusion reactions; however, there may be variability for individual donors.

In an assay of hemolytic potential using human whole blood, GEN1046 did not cause hemolysis and was also compatible with human whole blood and plasma at concentrations ≤500 µg/mL. In limited safety pharmacology evaluations in the Good Laboratory Practice (GLP) toxicity study (electrocardiograms [ECGs]/heart rate, neurobehavioral), GEN1046 had no adverse effects.

In the non-GLP single-dose exploratory toxicology study, GEN1046 by intravenous (IV) infusion to female monkeys at dose levels up to 30 mg/kg was well tolerated and not associated with any adverse changes. CCI [redacted]

In the first GLP repeat-dose toxicity study, GEN1046 was administered by IV infusion once (1 dose) every 3 weeks (1Q3W) on Days 1 and 22 (1Q3Wx2) to cynomolgus monkeys. Overall, IV infusion of GEN1046 on Days 1 and 22 to male and female cynomolgus monkeys did not induce any adverse GEN1046-related changes in in-life parameters, macroscopic or microscopic changes, any sign of local intolerance, and nothing was indicative of a cytokine release syndrome. No GEN1046-related findings were noted after a 4-week recovery phase. CCI [redacted]

CCI [redacted] the no-observed-adverse-effect level (NOAEL) and highest non-severely toxic dose for GEN1046 are considered 30 mg/kg CCI [redacted]

In the second GLP repeat-dose toxicity study, GEN1046 was administered by IV infusion weekly for 14 doses to cynomolgus monkeys. As for the 1Q3Wx2 study, IV infusion of GEN1046 to male and female cynomolgus monkeys did not induce any adverse GEN1046-related changes in in-life parameters or macroscopic or microscopic anatomical changes, nor was there evidence of local intolerance or cytokine release syndrome. No GEN1046-related findings were noted after an 8-week recovery phase. Overall, no new or more severe findings were observed compared to the 1Q3Wx2 study. CCI [redacted]

For more comprehensive information related to the nonclinical studies for GEN1046, please refer to the Investigator's Brochure (IB).

2.1.4 Summary of Clinical Trials

This is the first clinical trial of GEN1046 in humans. Refer to the current version of the IB for preliminary data.

2.2 Rationale

There is a strong unmet medical need to develop new efficacious therapies for patients with advanced malignancies.

Over recent years, clinical data have emerged on different mechanisms to activate the immune response against malignant cells. These observations have been rapidly advanced into effective immunotherapies. One successful strategy is to counteract immunosuppressive signals produced by cancer cells or cells in the tumor microenvironment (TME) with mAbs that target inhibitory receptors on immune effector cells, eg, PD-1, or their ligands (eg, PD-L1). Agents designed to block the inhibitory immune checkpoints, PD-1 or PD-L1 were first approved in melanoma and later in other types of cancers (Hodi et al., 2010; Ribas and Wolchok, 2018). However, durable clinical responses are observed only in a limited number of patients and overcoming resistance remains a major challenge. Therefore, the combined targeted approach of a bispecific antibody may be necessary to improve the clinical benefits observed with PD-1/PD-L1 monotherapy.

4-1BB is a costimulatory member of the TNF receptor superfamily and is expressed on a variety of immune cells following activation, including T cells, dendritic cells, and natural killer (NK) cells (Bartkowiak and Curran, 2015; Cheuk et al., 2004; Croft, 2009). Engagement of 4-1BB by its ligand leads to potentiation of effector immune responses (Bartkowiak and Curran, 2015). Crosslinking of 4-1BB by soluble 4-1BBL, 4-1BBL-expressing cells or agonist anti-4-1BB antibodies induces cytokine production, including IFNγ and TNFα, prevents activation-induced cell death of T cells, and upregulates cytotoxic T-cell effector functions (Bartkowiak and Curran, 2015). In patients with cancer, 4-1BB expression on recently activated $CD8^+$ T cells has been used to identify tumor-antigen specific T cells in peripheral blood or tumor-reactive tumor-

infiltrating lymphocytes (TILs) (Parkhurst et al., 2017; Wolfl et al., 2007; Ye et al., 2014), suggesting a role for 4-1BB in the anti-tumor immune response. Furthermore, combining 4-1BB agonists with PD-1 blockade has been shown to produce additive or synergistic anti-tumor activity in solid tumor models including both human TIL and mouse models (Tolcher et al., 2017).

Currently, no 4-1BB-targeting antibodies have been approved for the treatment of cancer. Several antibodies targeting 4-1BB are currently in clinical development for the treatment of hematological and solid tumors, including utomilumab and urelumab (Ascierto et al., 2010; Bartkowiak and Curran, 2015). While 4-1BB-targeted therapies have shown promising results in nonclinical tumor models (extensively reviewed in (Bartkowiak and Curran, 2015)), clinical development of 4-1BB has been delayed by hepatic toxicity. The mechanism involved in producing urelumab-related hepatic toxicity is not yet completely understood however, preliminary data from nonclinical toxicity models suggests hepatic infiltration by lymphocytes following crosslinking of 4-1BB receptor as being possibly involved in producing liver toxicity (Segal et al., 2017).

The MoA of GEN1046 is distinct from that of conventional PD-L1-blocking and 4-1BB-targeting IgG mAbs, as well as combination treatments thereof. Although the PD-L1-specific arm of GEN1046 functions as a classical CPI by blocking the PD-1/PD-L1 axis also in the absence of 4-1BB binding, the addition of a 4-1BB-stimulating arm further enhances T-cell activation. Conventional 4-1BB-targeting antibodies are typically dependent on direct agonist activity or agonist activity through FcγR-mediated crosslinking of antibodies on the cell surface. GEN1046, however, contains a silenced Fc region that does not bind to FcγR or complement factor C1q, thereby preventing cytotoxic activity through FcγR-mediated effector functions and 4-1BB agonist activity through FcγR-mediated crosslinking of membrane-bound GEN1046. As GEN1046-mediated signaling of 4-1BB on activated T cells is strictly dependent on simultaneous binding of the PD-L1-binding arm, the toxicity of GEN1046 is expected to significantly differ from conventional antibodies targeting 4-1BB, which also lead to cellular activation in the absence of PD-L1 expression in the near vicinity.

2.2.1 Rationale for Combining with Docetaxel

For the docetaxel combination cohort, initial evaluation of safety of GEN1046 in combination with docetaxel will be conducted in subjects with metastatic NSCLC who have progressed on platinum-based chemotherapy and PD-L1 inhibitor therapy. The synergistic activity of docetaxel and GEN1046 has not been evaluated in prior trials; however, chemotherapy combinations with PD-L1 inhibitors have shown promising results (Gandhi et al., 2018).

Subjects will be treated with GEN1046 100 mg 1Q3W in combination with 55 mg/m^2 on the first dose level of docetaxel and subsequently, if no more than 1 subject experiences dose-limiting toxicity (DLT) on that dose level, the dose of docetaxel will be increased to 75 mg/m^2.

The GEN1046 dose of 100 mg 1Q3W used for the combination treatment is the RP2D, determined in the dose escalation part of the trial. In the dose escalation portion of the trial, no MTD was determined, and doses up to 1200 mg 1Q3W were administered safely. The determination of dose is based on the totality of the available clinical efficacy and safety data, and the magnitude and consistency of immune modulation of pharmacodynamic endpoints and PK/pharmacodynamic model predictions. Initial safety data indicate that the occurrence of the most frequent adverse events (AEs) such as alanine aminotransferase (ALT)/aspartate

aminotransferase (AST) elevations are not dose proportional and would therefore not require a lower starting dose for GEN1046 for safety reasons. Preliminary efficacy is observed at doses of 80 to 200 mg 1Q3W, and clinical pharmacodynamic endpoints indicate consistent modulation of proliferating ($Ki67^+$) effector memory $CD8^+$ T cells and circulating levels of IFNγ at dose levels of ≤200 mg 1Q3W. These results are in line with predicted optimal trimer formation and average receptor occupation for PD-L1 blockade in tumor, which was observed at doses in the range of 80 to 140 mg 1Q3W using mechanistic modeling. The most frequent AEs reported in subjects receiving GEN1046 are transaminase elevations, followed by hypothyroidism, fatigue, nausea, asthenia, and neutrophil count decrease. Although mild or moderate increase of transaminases has been reported in patients with NSCLC receiving 75mg/m^2 of docetaxel, these are not frequently seen side effects (Herbst et al., 2016). Other common side effects of docetaxel, which overlap with adverse reactions seen with GEN1046, include fatigue, nausea, asthenia, and neutrophil count decreased. However, these events are not seen as frequently with GEN1046 as they are with docetaxel, and the vast majority of the events are mild or moderate.

2.2.2 Rationale for Evaluation of GEN1046 in Combination with Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed death-ligand 2 (PD-L2) releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Pembrolizumab is in clinical development for treatment of advanced malignancies (Merck, 2021). Pembrolizumab is indicated for the treatment of patients with metastatic NSCLC as monotherapy or in combination with chemotherapy.

For patients with untreated, advanced, or metastatic NSCLC, anti-PD-(L)1 monotherapy has demonstrated superior efficacy compared to chemotherapy in high PD-L1 expressors (tumor proportion score [TPS] ≥50%), and to a lesser extent in low PD-L1 expressors (TPS 1% to 49%). Pembrolizumab has US approval in patients with TPS ≥1%; however, there is still a need to improve and prolong the efficacy of CPI monotherapy in 1L NSCLC without driver mutations in patients with both high and low PD-L1 expressing tumors.

Since 4-1BB is often co-expressed with PD-1 on PD-1+ T cells, blockade of PD-L1/PD-1 as well as PD-L2/PD-1 signals and simultaneous co-stimulation through 4-1BB may synergize to enhance T-cell effector functions and improve the duration of the response (Kim et al., 2019). Based on PK/pharmacodynamic modeling data of GEN1046 as monotherapy and in combination with pembrolizumab, GEN1046 doses that favor peak trimer formation (crosslinking of GEN1046 to PD-L1 and 4-1BB) will result in higher 4-1BB activation, but only partial PD-L1 receptor occupancy (RO), whereas higher doses of GEN1046 will favor PD-L1 RO at the expense of optimum 4-1BB activation. Therefore, combining GEN1046 at a dose that favors 4-1BB conditional agonism with an agent that fully blocks the PD-1 interaction with both PD-L1 and PD-L2 may allow for more effective concurrent targeting of the 4-1BB and PD-1 pathways. The combination of GEN1046 with pembrolizumab is supported by nonclinical experiments. The combination of GEN1046 with pembrolizumab enhanced CD8+ T-cell expansion and cytokine production in vitro compared to each agent alone. Furthermore, in the MC38 in vivo tumor model, a mouse-reactive PD-L1x4-1BB antibody combined with an anti-mouse PD-1 antibody induced more potent anti-tumor activity compared to each agent as monotherapy and resulted in complete tumor regressions in the majority of mice tested. Importantly, the combination conferred protection against secondary tumor challenge, consistent with response durability and lasting immune memory in vivo. For more comprehensive information related to

the nonclinical studies on the combination of GEN1046 with pembrolizumab, please refer to the current version of the IB.

Collectively, these results provide rationale for combining GEN1046 with an anti-PD-1 agent like pembrolizumab to further amplify the anti-tumor immune response. As overlapping toxicities cannot be ruled out (see Section 7.3.7.1), a careful safety run-in and evaluation will be conducted before randomizing subjects to treatment with GEN1046 in combination with pembrolizumab (see Section 4.1.2.2).

2.2.2.1 Rationale for Evaluation of GEN1046 in Combination with Pembrolizumab and Platinum-based Chemotherapy Doublets

Results of the phase 3 Keynote-189 and Keynote-407 trials comparing SOC chemotherapy to pembrolizumab + SOC chemotherapy in patients with previously untreated metastatic non-squamous and squamous NSCLC demonstrated superior efficacy (OS at 12 months, median PFS, and response rate) for the pembrolizumab combination group versus the chemotherapy only group. Furthermore, improvement was noted across all PD-L1 categories evaluated (Gandhi et al., 2018; Paz-Ares et al., 2018). The addition of pembrolizumab in Keynote-189 did not appear to increase the frequency of AEs that are commonly associated with chemotherapy regimens involving pemetrexed and a platinum-based drug. Similarly, the incidence of most immune-mediated AEs was not higher with pembrolizumab combination therapy than that previously observed with pembrolizumab monotherapy. In Keynote-407, the AE profile observed was as expected on the basis of the known events associated with pembrolizumab, carboplatin, paclitaxel, and nab-paclitaxel, with no new safety signals identified.

Despite improvements in clinical outcomes for patients treated with pembrolizumab in combination with chemotherapy or pembrolizumab alone, only about half or fewer patients respond to treatment and, for the majority of patients, the responses are not durable. Therefore, there is a need to improve the SOC options of pembrolizumab monotherapy or in combination with chemotherapy in patients with 1L NSCLC without driver mutations across PD-L1 expression levels. In EC12 and EC13, GEN1046 will be explored as an add-on to the approved SOC of pembrolizumab + platinum-based chemotherapy doublets per tumor histology in PD-L1 all comers.

Treatment with GEN1046 is already being explored in combination with docetaxel or pembrolizumab (refer to Sections 2.2.1 and 2.2.2). CCI [redacted] As overlapping or unexpected toxicities, however, cannot be ruled out, a careful safety run-in and safety evaluation will be conducted for each chemotherapy backbone+GEN1046+pembrolizumab before initiation of the main cohorts (see Section 4.1.2.3).

2.3 Benefit-Risk Assessment

2.3.1 GEN1046

Based on nonclinical and preliminary clinical data, the benefit-risk ratio is considered positive for trial GCT1046-01. Patients with limited or potentially less effective treatment options of

limited duration and for whom the investigator agrees that clinical trial participation is appropriate may benefit from treatment with GEN1046 monotherapy or GEN1046 in combination.

Durable clinical benefit has been observed in the clinic in a subset of patients with several PD-1/PD-L1 inhibitors. Previous clinically tested human PD-L1 inhibitors have generally been well tolerated and most AEs have been mild to moderate (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v5.0 (NCI-CTCAE, 2017), grade 1-2). AEs associated with PD-L1 targeted therapy may be of immunologic etiology and are commonly referred to as immune-related adverse events (irAEs). PD-L1-targeted therapy can usually continue in the presence of mild irAEs with close monitoring; however, moderate to severe irAEs have been reported and require close monitoring and proper management (Brahmer et al., 2018; Schneider et al., 2021).

There is limited safety data available for mAbs targeting 4-1BB. An integrated safety analysis of early clinical trials conducted with urelumab based on 346 exposed subjects revealed that elevated AST and ALT were the most frequent TRAEs (in the range of 10% to 25%), with a rate of 3.6% at 0.3 mg/kg for both and a rate of 13.5% and 16.6% for AST and ALT at doses of 1.0 mg/kg and higher (Segal et al., 2017). Of note, there was 1 case of acute hepatitis observed out of 56 patients exposed at 0.3 mg/kg. All other AEs ≥ grade 3 were below 10% with neutropenia being the highest at a rate of 6%. However, it should be considered that conventional 4-1BB-targeting antibodies are typically dependent on direct agonist activity or agonist activity through FcγR-mediated crosslinking of antibodies on the cell surface, whereas GEN1046 is distinct from other mAbs in development. This is because 4-1BB is only conditionally activated, as it is dependent on simultaneous PD-L1 binding, which is why the safety profile may differ.

Preliminary Efficacy

The efficacy evaluation is based on data from the completed dose escalation part in the ongoing GCT1046-01 trial. Anti-tumor activity across different dose levels was observed as late-line therapy in these subjects with non-central nervous system (CNS) solid tumors with no available SOC, including those resistant to prior immunotherapy and those with tumors typically less sensitive to immune CPIs. Refer to the current version of the GEN1046 IB for additional efficacy information.

Safety

Overall, the safety profile of GEN1046 has been acceptable across the dose escalation and expansion parts of the GCT1046-01 trial. Refer to the current version of the GEN1046 IB for additional safety information.

GEN1046 is an immunomodulatory agent and, based on its MoA, irAEs have been observed. Immune-mediated liver toxicity is the most frequently observed irAE with GEN1046 treatment. In general, hepatic events (AST/ALT elevations) have been asymptomatic, manageable, and reversible with treatment delay of GEN1046 and steroid treatment.

Hyperinflammatory syndromes, including hemophagocytic lymphohistiocytosis (HLH), an uncommon adverse reaction, and cytokine release syndrome (CRS) have been reported in GEN1046 trials. While these events are uncommon with GEN1046 treatment, they can be

potentially serious, leading to severe or even fatal outcomes if not properly diagnosed and managed.

A mitigation plan for handling AEs, in particular for elevated liver laboratory parameters, irAEs, hyperinflammatory syndromes, and infusion-related reactions (IRRs), has been prepared for this trial in order to closely monitor, dose-delay, or withdraw subjects based on AEs that may occur with PD-L1 and 4-1BB targeted agents (please see Section 7 and Table 7-1).

GEN1046 is explored in combination with approved SOC regimens like pembrolizumab and chemotherapies with well-known safety profiles in dedicated cohorts of this trial. The risk of potentially overlapping toxicities has been carefully assessed for each regimen and a cautious safety run-in and elaborate safety evaluation will be conducted for each combination regimen before opening the main cohort. As additional risk mitigation measures, close monitoring of the subjects, particularly during the first 4 cycles of treatment will be applied together with clear recommendations for adequate and prompt management of potential toxicities (see Sections 6 and 7). Based on nonclinical and clinical data available to date, and published data from other human 4-1BB and PD-L1 mAbs, the conduct of the trial GCT1046-01 is regarded as justifiable and the benefit-risk profile favorable for GEN1046 in the oncologic setting.

The patient populations eligible for the current trial are either subjects with selected advanced and/or metastatic cancer, who have failed available standard therapy or who are not candidates for standard therapy, or CPI-naïve subjects with newly diagnosed metastatic NSCLC who will be offered GEN1046 monotherapy or GEN1046 as addition to the current SOC, and for who in the opinion of the investigator, experimental therapy with GEN1046 may be beneficial. All subjects enrolled in this trial will be monitored by qualified health care professional(s) who will provide care and evaluate the subject's response to the trial drug, in terms of its safety and efficacy.

More detailed information about 4-1BB and PD-L1 receptor expression, nonclinical and clinical trial results, potential safety aspects, and the known and expected benefits and risks including reasonably expected AEs of GEN1046 therapy can be found in the current version of the GEN1046 IB.

3 OBJECTIVES AND ENDPOINTS

Objectives and related endpoints are described in Table 3-1 and Table 3-2.

Table 3-1 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) (dose escalation only) • 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	• PK parameters
• Evaluate immunogenicity of GEN1046	• Anti-Drug Antibody (ADA) response

• Evaluate anti-tumor activity	• 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	• 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
• Evaluate efficacy	• 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 3-2 Objectives and Endpoints – Expansion Cohort EC1

Objectives	Endpoints
Primary	
• Evaluate clinical efficacy	• Objective Response Rate (ORR) per RECIST 1.1
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 • 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 • To assess anti-tumor activity based on iRECIST	• Immune system activation (eg, immune subset shift, tumor immune cell infiltration etc) • 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.

4 TRIAL DESIGN

4.1 Description of Trial Design

Please note: Any elements in the protocol that are only applicable to sites in certain regions are clearly marked as such in Table 17-2 and are not applicable to sites in other regions.

This is an open-label, multicenter phase 1/2a dose escalation, safety, and PK trial of GEN1046 in a mixed population of subjects with solid tumors. The trial consists of 2 consecutive parts: a FIH dose escalation (phase 1) and an expansion (phase 2a). In the dose escalation, subjects will receive one infusion of GEN1046 1Q3W until protocol-defined treatment discontinuation criteria are met (refer to Section 8.1). Different doses and schedules might be explored during the dose escalation and/or expansion based on the data generated in the dose escalation. Efficacy will be assessed by on-treatment imaging every 6 weeks (±7 days) for 50 weeks, and every 12 weeks (±7 days) thereafter until disease progression is assessed by the investigator (unless the investigator elects to continue treatment and follow immune Response Evaluation Criteria in Solid Tumors [iRECIST]), the start of new anti-cancer therapy, withdrawal of consent, or death, whichever occurs first. The RECIST 1.1 criteria will be used for secondary endpoint response evaluation (Eisenhauer et al., 2009); iRECIST will be used for exploratory endpoint response evaluation (Seymour et al., 2017). If the investigator elects to apply iRECIST, treatment should continue until disease progression has been verified (refer to Section 9.2.2).

Dose escalation explores a 1Q3W dose schedule. The concept of the design of the trial is shown in Figure 1-1. A more detailed description is provided in Section 4.1.1.

The expansion (phase 2a) is planned to consist of up to 13 cohorts, mainly to provide additional safety, and initial efficacy information as well as more detailed data related to the MoA.

4.1.1 Dose Escalation

The dose escalation starts with an accelerated phase consisting of single subject cohort(s) followed by larger subject cohorts informed by the modified Continuous Reassessment Method (mCRM) and Escalation with Overdose Control (EWOC) design. The single subject cohort(s) will be expanded to 3-subject cohorts in case of occurrence of toxicities defined in Section 7.1 or based on the decision of the sponsor's Safety Committee (SC). In addition, in the single subject cohort phase, the next cohort can start only once the DLT period for the previous dose level has been assessed and the next dose level is proposed by the Dose Escalation Committee (DEC) and endorsed by the SC. To supplement routine safety monitoring by the SC as outlined in this protocol, a Data Monitoring Committee (DMC) will monitor safety data for the trial on a quarterly basis or more frequently as determined by the sponsor. Additional details regarding DEC, SC, and the DMC can be found in Section 10.9 and Section 10.10.

There will be a minimum of 2 nights between the first and second subject in each dose cohort to account for any acute safety signals in each new dose level. An overnight stay will be required for the first subject in each dose level and may be required for additional subjects and/or dose levels if recommended by the sponsor SC. Furthermore, no other subjects within a dose cohort will receive their first treatment simultaneously, ie, on the same day, during dose escalation, except for dose levels declared safe by the SC which are further investigated. During treatment in dose escalation, safety assessments will be performed at least weekly in the first 2 cycles, on a

weekly basis for Cycles 3 to 4, and thereafter every 3 weeks. For the assessments of each cohort the DLTs will be collected for the first treatment cycle, ie, a DLT evaluation period of 21 days.

In the mCRM, the relationship between probability of DLT and dose level will be described by a Bayesian logistic regression model (BLRM). After each cohort the model parameters will be updated based on the available DLT information and a next dose suggested based on the posterior probability of DLT at each dose.

The 1Q3W dose escalation will potentially (dependent on data collected during the trial) evaluate GEN1046 at 7 main dose levels: 25, 80, 200, 400, 800, 1200 and 1600 mg, and 6 optional intermediate dose levels: 50, 140, 300, 600, 1000 and 1400 mg.

All escalations are constrained: Escalation can only be made to a new dose level no more than 1 step higher than a dose level (intermediate dose levels will count as half a step) previously investigated in the trial. De-escalations can skip dose levels. The dose escalation is limited to only main dose levels until the first DLT is observed; thereafter the intermediate dose levels become available.

The following provides a description of the procedure for subject accrual and provisions for dose escalation/de-escalation decisions.

1. After completion of Cycle 1 of each cohort, based on the safety data and the BLRM; the SC will decide on the dose level for the next cohort of subjects.
2. The initial dose levels will be single subject cohorts. This is the accelerated part and this single-subject cohort may be optionally expanded with up to 2 additional subjects for the purpose of obtaining additional safety, PK, pharmacodynamic, and biomarker data. During the dose escalation phase, if subjects in one of these cohorts have experienced an AE that fulfill the DLT criteria at any time, nonhematologic ≥ grade 2 drug-related toxicities (if baseline < grade 1), ≥ grade 2 drug-related hepatotoxicity (transaminases and/or bilirubin) or ≥ grade 2 drug-related CRS, it will be mandatory to increase the cohort size to at least 3 evaluable subjects for the currently enrolling and subsequent cohorts. If 2 or more subjects have already been allocated to a higher dose level, the SC will be consulted. This marks the start of the standard titration part.
3. A subject will be considered as evaluable for dose determination if they experience a DLT during Cycle 1 or meet the minimum treatment and safety evaluation requirements for the first cycle (refer to Section 7.1).
4. A 2-parameter BLRM with overdose control principle will be used to support recommendations on the next dose level, with the following 3 exceptions:
    - For cohorts requiring ≥3 evaluable subjects, if only 2 evaluable subjects are available for assessment (all others drop out) and neither subject has experienced a DLT, 2 subjects will be considered sufficient for decision-making.
    - If 2 subjects in a cohort experience DLTs, the BLRM model will be updated and re-evaluated before the enrollment of any additional subject.

- If a decision has been made to escalate to a higher dose level, but 1 or more additional subject(s) treated at preceding dose levels (see provision 8) experience(s) a DLT in Cycle 1, then the BLRM will be updated before any additional subject is enrolled to the current (higher) dose level.

5. Following the principle of EWOC, the BLRM model only allows escalation to dose levels which are likely to be safe.
6. For further understanding of the safety, tolerability, and PK of GEN1046, additional cohorts of up to 9 subjects may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation or even thereafter.
7. A cohort may be expanded to enroll up to 2 additional subjects, if such subjects can be enrolled no later than 28 days after treating (first dose of) the required minimum number of subjects for the cohort. This in order to ensure sufficient data due to the potential for subjects to discontinue therapy during Cycle 1 without DLT (eg, because of early disease progression) and allow flexibility.
8. After repeating the above steps, the MTD is declared when at least 9 subjects have been evaluated at a dose level and the BLRM recommends allocating an additional cohort to the same dose level. This dose level is the MTD identified by the mCRM.
9. The dose escalation stops when either the MTD has been declared, no doses are considered safe, or a certain number of subjects (N_{min}=30 and N_{max}=100) has been enrolled.

   More details on the continual reassessment method (CRM) and criteria for overdose control (when a dose is considered safe) can be found in Section 11.2.1.

After completion of the DLT period for each cohort, the DEC will review the data from the DLT period including but not limited to all relevant safety, clinical, PK, and biomarker data to propose the next dose. Thereafter, the sponsor SC will endorse the dose level for the next cohort of subjects.

The RP2D will be based on a review of the available safety and dosing information (including AEs, safety laboratory values, pharmacodynamic markers, and observations made after the end of the DLT evaluation period) and may be lower than the MTD.

4.1.2 Expansion

The aim of the expansion is to provide further data on the safety, tolerability, MoA, PK and anti-tumor activity of the selected dose/schedule. In addition, alternative doses/schedules may be tested in the expansion.

Recruitment will be initiated in up to 6 tumor types, ie, in NSCLC, endometrial cancer, UC, TNBC, SCCHN, and cervical cancer in 12 parallel cohorts (see Table 1-1). In Expansion Cohorts EC1 to EC13, efficacy analysis will begin after at least 10 treated subjects having minimally sufficient data (either discontinued GEN1046 treatment or having at least 1 post-baseline imaging assessment) for objective response evaluation. If there is evidence of anti-tumor activity such as tumor shrinkage or prolonged disease stabilization, and without safety concerns, up to 40 subjects will be allocated to each expansion cohort from EC2 to EC7 and EC10. Up to 40 subjects will be allocated to Cohort EC8, up to 32 subjects will be allocated to Cohort EC9, and up to 140 subjects will be allocated to Cohort EC1. After a safety run-in including at least 6

subjects, up to 40 subjects will be randomized and allocated to either EC11A or EC11B (20 in each) with the possibility to expand to 80 subjects in total if the benefit-risk assessment is favorable. After a safety run-in including at least 6 subjects for each cohort, up to a total of 40 subjects will be enrolled to EC12 or EC13, respectively, depending on tumor histology. Further expansion cohorts in additional tumor types may be opened based on preliminary efficacy signals generated in the dose escalation. The sponsor will determine the priority of opening the disease-specific expansion cohorts based on the data obtained in the dose escalation. Enrollment of PD-L1 negative or indeterminate subjects may be limited based on emerging efficacy and biomarker data.

For the purposes of this protocol, refractory is defined as having a best overall response (BOR) of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks.

No more than 52 of 140 subjects who are refractory to PD-1/L1 therapy may be enrolled in Cohort EC1 and no more than 15 of 40 subjects who are refractory to PD-1/L1 therapy may be enrolled in Cohorts EC3, EC5, EC6, and EC10, respectively. Sponsor medical monitor approval is required for enrollment for subjects with PD-1/L1 refractory disease. Based on data available and if deemed appropriate, a RP2D may be declared and expansion cohorts may be initiated before the MTD has been reached. Furthermore, different doses and schedules might be explored in the expansion cohorts.

In the expansion, a DMC risk-benefit analysis will be performed at pre-specified intervals as defined in the DMC Charter. The DMC and the sponsor SC will evaluate the safety profile with particular emphasis on any safety signals. Additional details regarding the DMC can be found in Section 10.9.

NSCLC Expansion Cohorts

In NSCLC expansion cohorts EC1, EC2, and EC10 at least 15 out of 140, 40, and 40 subjects, respectively, should have squamous histology. Enrollment may be exceeded to ensure adequate representation of both non-squamous and squamous histologies in the analysis.

Since response rates and other disease-related outcomes are expected to widely differ in a PD-1/PD-L1 naive population vs a PD-1/L1 pretreated population, patients with NSCLC were separated into different cohorts to ensure sufficient evidence of preliminary efficacy. Furthermore, while PD-1/L1-targeted agents alone or in combination have gained approvals in NSCLC in several countries and in several treatment settings, many countries still lack or restrict access. Cohort EC1 and EC2 aim to explore the safety and preliminary efficacy in PD-1/L1-pretreated and PD-1/L1-naive patients, respectively, both in the 2L+ metastatic setting of NSCLC. If preliminary clinical evidence suggests a substantial improvement over available therapies in a population with high unmet medical need (eg, PD-L1 low or negative) as determined by the DMC's review of the totality of the data, the sponsor may request to open Cohort EC2 in areas where access to PD-1/L1 inhibitors is not restricted.

There is evidence for a relationship between tumor PD-L1 expression and treatment benefit with PD-1/L1 inhibitors. In EC8, the potential association between treatment effect and PD-L1+ tumor status will be explored in patients naive to prior treatment with a PD-1/L1 inhibitor in the 1L setting of metastatic NSCLC. The cohort will be analyzed in 2 strata (PD-L1 + low [TPS 1% to 49% or 1% to 49% tumor cells for CCI scoring algorithm (TC)]

and PD-L1 + high [TPS ≥50% or ≥50% TC]) based on retrospective, central PD-L1 expression level in the tumor.

In EC10, the potential association between treatment effect and PD-L1+ tumor status will be investigated in subjects with advanced/metastatic NSCLC pretreated with PD-1/L1 inhibitor. CCI

An activation/maintenance dosing schedule of GEN1046 will be investigated in both EC8 and EC10 (see Section 4.4.1.2).

In EC9, the combination of GEN1046 and docetaxel will be investigated in subjects with NSCLC pretreated with PD-1/L1 inhibitor (see Section 4.1.2.1).

In EC11 cohorts, the combination of GEN1046 and pembrolizumab will be investigated in the 1L setting in subjects with PD-L1+ (TPS ≥1% or ≥1% TC) tumors. CCI

In EC12 and EC13 cohorts, the combination of GEN1046 and pembrolizumab and relevant platinum-based chemotherapy doublets will be investigated in the 1L setting in subjects with non-squamous (EC12) or squamous (EC13) metastatic NSCLC who are CPI-naïve and unselected for tumor PD-L1 expression. Dosing will be as described in Section 4.4.2. The study design is illustrated in Figure 1-4 and Section 4.1.2.3.

CCI

UC Expansion Cohort

The UC cohort will include both subjects who are eligible to receive platinum-based chemotherapy and subjects who are not eligible to receive platinum-based chemotherapy. Up to 15 subjects who are not eligible to receive platinum-based chemotherapy may be enrolled into Cohort EC3b. All other UC subjects will be enrolled in Cohort EC3a.

SCCHN and TNBC Expansion Cohorts

The SCCHN and TNBC cohorts may include both subjects who have received prior treatment with a PD-1/PD-L1 inhibitor and subjects who have not received treatment with a prior PD-1/L1 inhibitor. At least 20 subjects shall be naive to PD-1/L1 treatment in Cohorts EC5 and EC6.

4.1.2.1 Expansion Cohort 9 – Docetaxel Combination

The docetaxel combination cohort will be a combination safety run-in and will enroll up to approximately 32 subjects who will be treated with GEN1046 combined with docetaxel. It will follow a 6 + 6 dose escalation design (Figure 1-2) which will evaluate the RP2D of GEN1046 at

100 mg in combination with 55 mg/m^2 and escalating to 75 mg/m^2 docetaxel. The maximum tested dose of docetaxel will be 75 mg/m^2, which is the approved dose for treatment of NSCLC.

Toxicity observed during the first cycle (ie, the DLT period) for the 6 subjects treated with a combination of GEN1046 100 mg and 55 mg/m^2 docetaxel (Dose level 1/DL1) will be evaluated by the DEC. If 0 or 1 DLT is observed in DL1, then the dose of docetaxel will be escalated, and 6 subjects will be treated with GEN1046 plus 75 mg/m^2 at DL2.

The safe combination dose level will be determined based on the totality of the safety data collected after the last subject treated in the dose escalation part has completed a minimum of 2 cycles. Once a dose level for the combination treatment has been determined, up to approximately 8 additional subjects will be enrolled to further evaluate for safety and preliminary efficacy.

4.1.2.2 Expansion Cohorts EC11A and EC11B – Pembrolizumab Combinations

According to a meta-analysis of 3526 patients for toxicity and response patterns with immunotherapy combinations, anti-PD-1/PD-L1 CPIs can be safely given with a variety of other immunotherapy and targeted agents (Nikanjam et al., 2017). GEN1046 dosed 1Q3W has an acceptable safety profile based on the monotherapy dose escalation part of the trial and the MTD has not been reached, demonstrating a broad safety range. Furthermore, based on PK modeling and simulation data, the peak of trimer formation of GEN1046 is predictive of the liver toxicity. However, the trimer formation is not dose proportional but instead in a bell-shaped curve and less frequent dosing with GEN1046 100 mg 1Q6W instead of 1Q3W is considered to lower trimer formation in the liver and potentially decrease the risk of liver toxicity while maintaining intermittent 4-1BB activation.

Therefore, 6 subjects will be enrolled sequentially in 2 cohorts of 3 subjects each during a preliminary safety run-in. The first 3 subjects will receive GEN1046 100 mg 1Q6W plus pembrolizumab 400 mg 1Q6W. They will be monitored closely and followed for a minimum of 3 weeks after which the DEC will make a preliminary safety assessment based on available data.

After the DEC has concluded that the 1Q6W regimen is considered safe, up to 6 additional subjects may be allocated to the 1Q6W cohort during the safety run-in of the 1Q3W cohort, in order to better understand the safety, tolerability, PK, pharmacodynamics, or anti-tumor activity of the 1Q6W regimen for which only limited data are available yet.

Once the 1Q6W regimen is declared safe, 3 subjects will be enrolled and treated with GEN1046 100 mg 1Q3W plus pembrolizumab 200 mg 1Q3W. These subjects will also be closely monitored and followed for a minimum of 3 weeks. After completion of the safety run-in, the collected data (including, but not limited to, all available safety data including potential DLTs and other relevant clinical data) will be evaluated by the DEC. If warranted, further safety evaluations or additional safety measures may be recommended by the DEC.

The design of the safety run-in is shown in Figure 1-3.

Only after the DEC review, and if the benefit-risk assessment of the combination regimen is considered acceptable based on the totality of data, enrollment to cohorts EC11A and/or EC11B will begin.

Approximately 40 subjects will be randomized to receive either:

- GEN1046 100 mg 1Q3W and pembrolizumab 200 mg 1Q3W (EC11A)
- GEN1046 100 mg 1Q6W and pembrolizumab 400 mg 1Q6W (EC11B)

CCI [redacted]

4.1.2.3 Expansion Cohorts EC12 and EC13 – GEN1046 in Combination with Pembrolizumab and Platinum-based Chemotherapy Doublets

Cohorts EC12 and EC13 will explore the safety and efficacy of GEN1046+pembrolizumab+platinum-based chemotherapy doublets in subjects with non-squamous or squamous, untreated, metastatic NSCLC, irrespective of PD-L1 expression level. CCI [redacted] To further safeguard subjects to be enrolled into cohorts EC12 and EC13, both cohorts will be initiated with a safety run-in.

The DEC will evaluate the toxicities observed in EC12 and EC13 during the first cycle (ie, the DLT period) and recommend to the SC whether to stay (S) and further enroll subjects into the safety run-in (unless the SC endorses to proceed to the full cohort), to close the safety run-in and expand (E) enrollment to the full cohort, or to discontinue (D) the safety run-in.

The safety run-in will be guided by a decision table derived from an "i3+3" design with a target toxicity rate $p_t = 0.3$ and the equivalence interval EI = [0.25,0.35]. Initially, 6 DLT-evaluable subjects will be assessed. Depending on the assessment of these subjects, up to an additional 6 subjects may be enrolled. Enrollment is dependent on the number of DLTs observed and the decision guided by Table 4-1. Subjects not evaluable for DLTs can be replaced at any time. Over-recruitment of the 6-subject cohort is allowed by 2 subjects to compensate for a potential screening failure of 33%. The DEC and SC are further detailed in Sections 10.10 and 10.10.1.3.

Table 4-1 Decision Table for Safety Run-in in EC12 and EC13

Number of Dose-limiting Toxicities	Number of Subjects						
	6	7	8	9	10	11	12
0	E	E	E	E	E	E	E
1	E	E	E	E	E	E	E
2	S	S	S	E	E	E	E
3	D	D	D	S	S	S	S
4	D	D	D	D	D	D	S
5	D	D	D	D	D	D	D

D (purple)=discontinue; E (blue)=expand enrollment further into full cohort (the regimen is declared safe); EC=expansion cohort; S (yellow)=stay (further enrollment into the safety run-in unless SC endorses to move to full expansion).

The decision to expand enrollment to the full cohort will be made on the totality of collected data (including, but not limited to, all available safety data including potential DLTs and other relevant clinical data). If warranted, further safety evaluations or additional safety measures may be recommended by the DEC or the SC.

4.2 Planned Number of Subjects

- 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]).

4.2.1 Replacement of Subjects

- Subject is not evaluable for DLTs (refer to Section 7.1)
- Subject was enrolled in the trial but did not receive a dose of GEN1046

4.3 Trial Design Rationale

The first part of this trial is a FIH, open-label, dose escalation safety trial studying GEN1046 in subjects with different types of malignant solid tumors in order to determine the safety profile of GEN1046.

In order to address the trial objectives in this FIH trial, a dose-escalation using an accelerated titration (ie, single-subject cohort) followed by an mCRM design was selected. Compared to

standard 3 + 3 and accelerated titration designs, the mCRM provides both more flexibility and better accuracy of the estimated MTD while safeguarding the subject's safety.

The second part of this trial is the expansion of tumor-specific cohorts for further investigation. The aim of the expansion is to provide further data on the safety, tolerability, PK, and anti-tumor activity of the selected dose as monotherapy or in combination in specific tumor types. In addition, alternative doses/schedules may be tested in the expansion part.

4.4 Rationale for Dose and Schedule of GEN1046

The starting dose of GEN1046 was based on an integrated approach considering the clinical experience with PD-L1 and 4-1BB targeted antibodies and the MoA of GEN1046, and was supported by the results from the GLP toxicity study in cynomolgus monkeys where the NOAEL was determined to be 30 mg/kg (1Q3W × 2, IV, 30-min infusion in saline). Based on PK modeling, the corresponding human dose CCI [redacted]. As a conservative approach, an additional safety factor of 10 was applied to this dose, resulting in a FIH starting dose of 25 mg (0.3 mg/kg) every 3 weeks for the GEN1046 FIH clinical trial.

The rationale for this FIH dose selection was further supported by the molecular nature of GEN1046 and the totality of the nonclinical data as supported by the following rationale:

- GEN1046 is a PD-L1×4-1BB bispecific antibody that is specifically engineered to induce conditional activation of T cells through 4-1BB stimulation, which is dependent on simultaneous binding to PD-L1. In addition, the PD-L1-specific arm of GEN1046 functions as a classical immune CPI by blocking the PD-1/PD-L1 axis. This MoA is intended to maximize anti-tumor efficacy while minimizing systemic toxicity.

- The MoA of GEN1046 is distinct from that of conventional PD-L1 and 4-1BB targeting IgG mAbs. Conventional 4-1BB-targeting antibodies are typically dependent on direct agonist activity, or agonist activity through FcγR-mediated antibody crosslinking. 4-1BB agonist activity by GEN1046 is conditional; it is dependent on simultaneous binding of GEN1046 to both 4-1BB and PD-L1. The Fc domain of GEN1046 was engineered to silence interactions with FcγR and complement factor C1q. Thereby, GEN1046-mediated stimulation of 4-1BB signaling in activated T cells is strictly dependent on the presence of PD-L1+ cells. Simultaneous binding to 4-1BB-positive T cells and PD-L1+ cells in the tumor or the lymph nodes allows GEN1046-mediated 4-1BB crosslinking. Binding of GEN1046 to 4-1BB in absence of PD-L1 does not induce agonist activity.

- The potential toxicity of GEN1046 was evaluated in cynomolgus monkeys, as this species was demonstrated to be the most relevant toxicology model based on in vitro studies. In these studies, GEN1046 was shown to bind to both cynomolgus monkey PD-L1 and 4-1BB, CCI [redacted].

- In the GEN1046 GLP toxicity study in cynomolgus monkeys, the NOAEL was determined to be 30 mg/kg (1Q3W × 2, IV, 30-min infusion in saline).

- Using a GEN1046 PK model and based on predicted systemic exposure in humans at comparable AUC in cynomolgus monkeys, the human dose corresponding to 30 mg/kg in

cynomolgus monkeys and applying a CCI [redacted]. As a conservative approach, an additional 10-fold safety factor was added resulting in a FIH dose of 0.3 mg/kg.

- The FIH dose starting dose selection considers the unique properties of GEN1046 that were engineered to mitigate potential safety risks identified with conventional PD-L1 and 4-1BB targeting IgG mAbs. Given the MoA of GEN1046 (in particular the conditional activation), the clinical experience with PD-L1 and 4-1BB targeted mAbs, and the intended patient population, the NOAEL-based approach with a 100-fold conservative safety factor was selected over the minimally-anticipated biological effect level (MABEL) approach. CCI [redacted]

- There is extensive clinical experience with PD-L1 inhibitors alone or in combination with 4-1BB targeted antibodies (Atkins and Thompson, 2018; Massarelli, 2017; Segal et al., 2017; Tolcher et al., 2017). To better understand the potential for CRS or IRRs that could occur upon administration of GEN1046, an in vitro cytokine release assay was performed suggesting a low likelihood for these events. This is consistent with the known safety profile for other PD-L1 and 4-1BB targeted agents previously tested in the clinic.

Based on these considerations, a starting dose of 25 mg 1Q3W was selected for the GEN1046 FIH clinical trial.

4.4.1 Rationale for Flat Dosing

An additional consideration for the development of GEN1046 is to initiate the FIH trial with flat dosing instead of body weight-based dosing. A flat dosing approach is desirable to facilitate drug preparation without the need to calculate the dose, per subject, thus lowering the potential risk of dosing errors as compared with body weight-based dosing. In addition, flat dosing also offers several advantages over weight-based dosing including better convenience and compliance, reduction of preparation time, and a reduced amount of drug waste. There are several examples of mAb based therapeutics that have either been developed using a flat dosing approach, or switched from body weight-based dosing to flat dosing either during clinical development or post-approval (Bai et al., 2012; Wang et al., 2009).

Furthermore, there is strong scientific rationale to support flat dosing of GEN1046. Monoclonal antibodies typically distribute to the blood plasma and extracellular fluids only, which increase less than proportionally with increase in body weight, and elimination takes place via proteolytic catabolism and intracellular degradation after binding to the target. Binding to the target is not related to body weight but mainly to tumor load, target expression levels in tumors vs endogenous expression, and affinity of mAb. In addition, intracellular degradation of mAbs targeting antigens at the cell surface is also not likely to be body weight dependent. Minor effects of body size on distribution and elimination of mAbs do not typically support body size-based dosing. Published simulation studies comparing the performance of a body size-based and flat dosing for several mAbs demonstrated that PK variability is expected to be similar between flat and body size-based dosing (Bai et al., 2012; Wang et al., 2009). In this trial, the starting dose of 0.3 mg/kg dose was converted to 25 mg dose based on a median body weight of 80 kg patient, and to present a distribution of body weights across oncology patients.

4.4.1.1 Rationale for Choosing 100 mg 1Q3W for Expansion Cohorts EC1-EC7 and EC9

The selection of the 100 mg 1Q3W dose was based on clinical data from the FIH trial, GCT1046-01, where doses ranging from 25 to 1200 mg 1Q3W were evaluated in 61 subjects in the dose escalation phase. In addition, a PK/pharmacodynamic model was developed to predict PD-L1 RO and 4-1BB, GEN1046, PD-L1 trimolecular complex (trimer) formation and RO for PD-L1 in tumors to understand the PK/pharmacodynamic/efficacy relationship.

4.4.1.2 Expansion Cohorts EC8 and EC10 – NSCLC Activation/Maintenance Dosing

Alternative doses/schedules may be tested in the expansion. Cohort EC10 will enroll subjects with advanced/metastatic NSCLC with PD-L1+ tumors pretreated with PD-1/L1 inhibitor who will receive the GEN1046 activation dose (100 mg) 1Q3W × 2 cycles ensuring early continuous 4-1BB activation followed by a higher maintenance dose (500 mg) of GEN1046 administered 1Q6W for subsequent cycles. An integrated semi-mechanistic physiologically based PK/pharmacodynamic model was used that incorporates dynamic binding of GEN1046 to PD-L1 and 4-1BB to predict trimer (crosslinking to PD-L1 and 4-1BB) formation and RO for PD-L1 in tumors. The model was then used to explore the predicted in vivo trimer formation and PD-L1 RO at various dosing regimens. The model shows that trimer formation in tumor peaks at a dose of GEN1046 100 mg 1Q3W, which is selected as the activation dose for 2 cycles. This will be followed by a maintenance dose of GEN1046 500 mg 1Q6W, which is predicted to provide higher PD-L1 RO over the dosing cycle and intermittent 4-1BB activation via engaging trimers in comparison to 100 mg 1Q3W.

A similar dosing regimen will be explored in the 1L setting of metastatic NSCLC in EC8 in patients with PD-L1+ tumors.

4.4.1.3 Expansion Cohorts EC11A and EC11B (GEN1046-Pembrolizumab Combinations)

Expansion Cohorts EC11A and EC11B will evaluate 100 mg GEN1046 in combination with pembrolizumab at 2 different dosing schedules:

- EC11A will test a GEN1046 regimen of 100 mg 1Q3W with a pembrolizumab regimen of 200 mg 1Q3W (for pembrolizumab 200 mg 1Q3W up to 35 cycles; total of 2 years). Based on PK/pharmacodynamic modeling, this regimen of GEN1046 is expected to result in peak trimer formation and sustained 4-1BB activation, which in combination with pembrolizumab may allow for optimum engagement of both targets/pathways and improved anti-tumor efficacy.
- EC11B will evaluate a GEN1046 regimen of 100 mg 1Q6W with a pembrolizumab regimen of 400 mg 1Q6W (for pembrolizumab 400 mg 1Q6W up to 18 cycles; total of 2 years). Based on PK/pharmacodynamic modeling, this regimen of GEN1046 is expected to provide intermittent/transient activation of 4-1BB in a 6-week dosing cycle compared to sustained 4-1BB activation in a 3-week dosing cycle. Transient activation of 4-1BB is expected to allow for resetting of the T-cell response and reduce chronic IFN signaling (Weber et al., 2021), which may prevent exhaustion of tumor-infiltrating CD8+ T cells due to continuous 4-1BB activation and, in combination with pembrolizumab, may provide improved DoR.

Pembrolizumab regimens of 200 mg 1Q3W and 400 mg 1Q6W have been approved as first- and second-line SOC treatment for NSCLC, respectively. Pembrolizumab 200 mg 1Q3W and 400 mg 1Q6W are expected to provide comparable efficacy and safety profiles (Lala et al., 2020).

4.4.2 Rationale for Dosing in EC12 and EC13 (GEN1046+Pembrolizumab+Platinum-based Chemotherapy Doublets)

Dosing regimens for pembrolizumab and the chemotherapies used in this trial for the non-squamous and squamous 1L NSCLC cohorts EC12 and EC13, respectively, represent the current SOC based on the efficacy and safety results from the phase 3 Keynote-189 and Keynote-407 trials (refer to Section 2.2.2.1).

GEN1046 will be added and administered at a dose of 100 mg 1Q3W. This is the RP2D GEN1046 dose and schedule determined from the dose escalation part of the trial.

In EC12 (non-squamous 1L NSCLC): Subjects will receive GEN1046 100 mg 1Q3W in addition to pembrolizumab 200 mg 1Q3W + platinum-based chemotherapy doublet:

- pemetrexed 500 mg/m^2 1Q3W
- +cisplatin 75 mg/m^2 1Q3W **OR** carboplatin AUC 5 mg/mL/min 1Q3W

for 4 cycles. CCI [redacted]

In EC13 (squamous 1L NSCLC): Subjects will receive GEN1046 100 mg 1Q3W in addition to pembrolizumab 200 mg 1Q3W + platinum-based chemotherapy doublet:

- carboplatin AUC 6 mg/mL/min 1Q3W
- +paclitaxel 200 mg/m^2 1Q3W (Day 1) **OR** nab-paclitaxel 100 mg/m^2 once (1 dose) every week (1Q1W) (Days 1, 8, and 15)

for 4 cycles. CCI [redacted]

4.5 Estimated Trial Duration, End of Trial, and End of Treatment Definitions

4.5.1 Estimated Trial Duration for an Individual Subject

The estimated trial duration for an individual subject is 74 weeks, consisting of a screening period of up to 35 days, an estimated average treatment period of 21 weeks (the duration of treatment may vary for each subject), and an estimated average post-treatment follow-up period of 11 months (the duration of follow-up may vary for each subject).

4.5.2 End of Trial

The end of trial is defined as the last date of data collection for the last subject in the trial globally.

The maximal trial duration is either 3 years after the last subject's first treatment or until all subjects have completed the second safety follow-up visit or started a new anticancer therapy or discontinued from the trial, whichever comes first.

4.5.3 Treatment Discontinuation

Treatment should continue until the subject fulfills one of the treatment discontinuation criteria (please see Section 8.1).

4.5.4 Trial Stopping Rules

If any of the below-listed events occur, a prompt cumulative review of safety data will be conducted by the sponsor SC to determine whether the trial will be discontinued permanently.

1) If at any time, all dose levels are considered unsafe as defined by the mCRM.

2) Any safety finding assessed as related to trial treatment that, in the opinion of the sponsor SC, contraindicates further dosing of trial subjects.

For each individual subject who has already received trial treatment and is currently in the trial at the time the trial stopping criteria are met, the risk/benefit whether to stop or continue treatment will be assessed. To allow continuation of treatment, DMC consultation will be considered. All subjects exposed to trial treatment should continue to be followed by the investigator for safety.

Where applicable, regulatory authorities and Independent Ethics Committees (IECs)/Institutional Review Board (IRBs) will be notified of any significant actions taken with the trial.

4.5.5 Trial Termination

The sponsor reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion.

The investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or ICH GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further trial drug development

Following end of trial (see Section 4.5.2) or trial termination, the sponsor will make their best effort to provide post-trial access to GEN1046 for those ongoing trial subjects continuing to derive treatment benefit**,** in accordance with local laws and requirements.

5 TRIAL POPULATION

5.1 Inclusion Criteria

Subjects are eligible to be included in the trial only if all of the following criteria apply:

Each potential subject must fulfill all of the following criteria to be enrolled in the trial.

For Dose Escalation:

1. Subjects must have a histologically or cytologically confirmed non-CNS solid tumor that is metastatic or unresectable and for whom there is no available standard therapy likely to confer clinical benefit, or subjects who are not candidates for such available therapy, and for whom, in the opinion of the investigator, experimental therapy with GEN1046 may be beneficial.

For Expansion:

2. Criterion amended as per Amendment 4
   2.1 Criterion amended as per Amendment 1
   2.2 Subjects must have histologically or cytological confirmed diagnosis of NSCLC, endometrial cancer, UC, TNBC, SCCHN, or cervical cancer that is relapsed or refractory, advanced and/or metastatic and for whom there is no available standard therapy or subjects are no longer candidates for or refuse standard therapy (if subjects had access and were eligible for the respective treatments), and for whom, in the opinion of the investigator, experimental therapy with GEN1046 may be beneficial. Subjects must have failed anti-cancer therapy as follows:

Expansion Cohort 1 (NSCLC): PD-1/L1 Pretreated (100 mg 1Q3W)

   a. Criterion amended as per Amendment 2.
      a1. Criterion amended as per Amendment 1_US-1/IL-1.
      a2. Criterion amended as per Amendment 1_EU-1.
      a3. NSCLC subjects who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of one treatment line) for metastatic disease with radiographic disease progression on or after last prior treatment.
   b. Criterion amended as per Amendment 2.
      b1. Criterion amended as per Amendment 1_US-1/IL-1.
      b2. Criterion amended as per Amendment 1_EU-1.
      b3. NSCLC subjects of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.
   c. Subjects should have received platinum-based therapy (or alternative chemotherapy due to platinum ineligibility, eg, a gemcitabine-containing regimen).
   d. Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor

approval is required for subjects with a BOR of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks.

e. Local results from the most recent PD-L1 test must be provided prior to enrollment. If local PD-L1 test results are unavailable, sponsor approval for enrollment is required.

Expansion Cohort 2 (NSCLC) – PD-1/L1-Naive

f. Criterion amended as per Amendment 2.
   f1. Criterion amended as per Amendment 1_US-1/IL-1.
   f2. Criterion amended as per Amendment 1_EU-1.
   f3. NSCLC subjects of any histology may be enrolled. NSCLC subjects who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of one treatment line) for metastatic disease with radiographic disease progression on or after last prior treatment.

g. Criterion amended as per Amendment 2.
   g1. Criterion amended as per Amendment 1_US-1/IL-1.
   g2. Criterion amended as per Amendment 1_EU-1
   g3. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.

h. Subjects should have received platinum-based therapy (or alternative chemotherapy due to platinum ineligibility, eg, a gemcitabine-containing regimen).

i. Subjects must not have received prior treatment with a PD-1/L1 inhibitor (refer to Section 4.1.2).

Expansion Cohort 3 (UC):

j. Criterion amended as per Amendment 2.
   j1. Criterion amended as per Amendment 1_US-1/IL-1.
   j2. Criterion amended as per Amendment 1_EU-1
   j3. UC (of the bladder, ureter, urethra, or renal pelvis) subjects with predominantly transitional-cell features on histology who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of one treatment line) for locally advanced/metastatic disease with radiographic disease progression on or after last prior treatment.

k. Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor approval is required for subjects with a BOR of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks.

l. Local results from the most recent PD-L1 test should be provided prior to enrollment (if available).

Cohort 3a: For Subjects Who Are Eligible to Receive Platinum-based Therapy:

m. Subjects must have received platinum-based chemotherapy.

Cohort 3b: For Subjects Ineligible to Receive Platinum-based Therapy:

n. Subjects must not be eligible for any platinum-based or any cisplatin-containing chemotherapy.

Expansion Cohort 4 (Endometrial Cancer):

o. Criterion amended as per Amendment 2.
   o1. Criterion amended as per Amendment 1_US-1/IL-1.
   o2. Criterion amended as per Amendment 1_EU-1.
   o3. Endometrial cancer subjects who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of one treatment line) for advanced/metastatic disease with radiographic disease progression on or after last prior treatment.
p. Subjects must have epithelial endometrial histology including: endometrioid, serous, squamous, clear-cell carcinoma, or carcinosarcoma.

   Note: Sarcomas and mesenchymal endometrial cancer are excluded.

q. Subjects must <u>not</u> have received prior treatment with a PD-1/L1 inhibitor (established local label/access need to be respected).
r. Local results of the most recent dMMR or MSI status as per local assessment should be provided prior to enrollment (if available).

Expansion Cohort 5 (TNBC):

s. Criterion amended as per Amendment 2.
   s1. Criterion amended as per Amendment 1_US-1/IL-1.
   s2. Criterion amended as per Amendment 1_EU-1.
   s3. TNBC defined as HER2-negative [HER2 is negative by fluorescence in situ hybridization] assay (non-amplified ratio of HER2 to CEP17 <2.0 single probe average HER2 gene copy number <4 signals/cell) <u>or</u> alternatively HER2 protein expression by IHC result is 1+ negative or IHC 0 – negative and ER and PgR negative status (defined as <1% of cells expressing hormonal receptors via IHC analysis) as per local assessment. Subjects who have received up to 4 prior systemic treatment regimens including but not limited to anthracycline-, taxane-, antimetabolite- or microtubule inhibitor-containing regimens (maintenance treatment is considered being part of one treatment line) for locally advanced/metastatic disease with radiographic disease progression on or after last prior treatment. Local pathological confirmation of triple-negative disease is required prior to trial entry.
t. Subjects with a prior history of a breast cancer with a different phenotype must have confirmation of TNBC from a biopsy obtained after the subject's last prior systemic therapy.

u. Local results of the most recent dMMR or MSI status as per local assessment should be provided prior to enrollment (if available).

Cohort 5a – Subjects Who Have Received Prior Treatment with a PD-1/L1 Inhibitor:

v. Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor approval is required for subjects with a BOR of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks.
w. Local results from the most recent PD-L1 test should be provided prior to enrollment (if available).

Cohort 5b – Subjects Who Have Not Received Prior Treatment with a PD-1/L1 inhibitor:

x. Subjects must not have received prior treatment with a PD-1/L1 inhibitor (established local label/access need to be respected).

Expansion Cohort 6 (SCCHN):

y. Criterion amended as per Amendment 2.
y1. Criterion amended as per Amendment 1_US-1/IL-1.
y2. Criterion amended as per Amendment 1_EU-1.
y3. Recurrent or metastatic SCCHN (oral cavity, pharynx, larynx) subjects who have received up to 4 prior systemic treatment regimens for recurrent/metastatic disease with radiographic PD on or after last prior treatment (maintenance treatment is considered being part of one treatment line).
z. Subjects must have disease progression on or after prior therapy with platinum-based chemotherapy (alternative combination chemotherapy is acceptable if the subject's platinum ineligibility status is documented).

Cohort 6a – Subjects Who Have Received Prior Treatment with a PD-1/L1 Inhibitor:

aa. Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor approval is required for subjects with a BOR of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks.

bb. Local results from the most recent PD-L1 test should be provided prior to enrollment (if available).

Cohort 6b – Subjects Who Have Not Received Prior Treatment with a PD-1/L1 Inhibitor:

cc. Subjects must not have received prior treatment with a PD-1/L1 inhibitor (established local label / access need to be respected).

Expansion Cohort 7 (Cervical Cancer):

dd. Criterion amended as per Amendment 2.
dd1. Criterion amended as per Amendment 1_US-1/IL-1.

dd2. Criterion amended as per Amendment 1_EU-1.

dd3. Cervical cancer subjects who have received up to 4 prior systemic treatment regimens including chemotherapy in combination with bevacizumab (according to the applicable labeling) unless the subject is ineligible for bevacizumab according to local standards (chemotherapy administered in the adjuvant or neoadjuvant setting, or in combination with radiation therapy should not be counted as a prior line of therapy) for recurrent/metastatic disease with radiographic disease progression on or after last prior treatment.

ee. Subjects must have cervical cancer of squamous cell, adenocarcinoma, or adenosquamous histology.

ff. Subjects must not have received prior treatment with a PD-1/L1 inhibitor (established local label / access need to be respected).

Expansion Cohort 9 (Docetaxel Combination [NSCLC]: GEN1046 in Combination with Docetaxel)

gg. Criterion amended as per Amendment 2.
gg1. Criterion amended as per Amendment 1_US-1/IL-1.
gg2. NSCLC subjects of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.

hh. Criterion amended as per Amendment 4.
hh1. Criterion amended as per Amendment 2.
hh2. Criterion amended as per Amendment 1_US-1/IL-1.
hh3. Subject has progressed during/after treatment with an anti-PD-1/L1 mAb administered either as monotherapy or in combination.
Note: Disease progression during/after anti-PD-1/L1 treatment is defined by meeting the following criteria:
- Has received at least 2 doses of an approved anti-PD-1/L1 mAb.
- Has demonstrated disease progression during/after PD-1/L1 as defined by RECIST 1.1.

ii. Criterion amended as per Amendment 4.
ii1. Criterion amended as per Amendment 2.
ii2. Criterion amended as per Amendment 1_US-1/IL-1.
ii3. Subjects have progressed during/after platinum doublet chemotherapy with or without an anti-PD-1/L1 mAb.

jj. Criterion added per Amendment 2.
jj1. No prior treatment with docetaxel. This includes past treatment with monotherapy, combination, and/or any experimental use.

Expansion Cohort 8 (NSCLC Treatment-Naive for Metastatic Disease: GEN1046 Monotherapy):

kk. Subjects with metastatic NSCLC who have received no prior systemic treatment regimens for metastatic disease. Subjects must not have received prior treatment with a PD-1/L1 inhibitor. Subjects must have radiographic disease progression on or after last prior treatment. This is not required for subjects who have newly diagnosed disease.

ll. Subjects with NSCLC of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.

mm. Criterion amended per Amendment 7
mm1. Prior to C1D1, subjects must have a PD-L1 expression result available from a tumor sample from the metastatic stage of the cancer. Tumor PD-L1 expression can be determined by the sponsor-designated central laboratory CCI [redacted] or per site local assessment with CCI [redacted] PD-L1 CCI assay used per manufacturer's instructions.

nn. Criterion amended per Amendment 7
nn1. Tumor demonstrates PD-L1 expression in ≥1% of tumor cells (TPS ≥1% or ≥1% TC) as assessed by IHC performed locally or by central laboratory testing.

Expansion Cohorts 11A and 11B (NSCLC Treatment-Naive for Metastatic Disease: GEN1046 in Combination with Pembrolizumab)

oo. Subjects with metastatic NSCLC who have received no prior systemic treatment regimens for metastatic disease. Subjects must not have received prior treatment with a PD-1/L1 inhibitor. Subjects must have radiographic disease progression on or after last prior treatment. This is not required for subjects who have newly diagnosed disease.

pp. Subjects with NSCLC of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.

qq. Criterion amended Amendment 7
qq1. Prior to C1D1, subjects must have a PD-L1 expression result available from a tumor sample from the metastatic stage of the cancer. Tumor PD-L1 expression can be determined by the sponsor-designated central laboratory CCI [redacted]

[redacted] or per site local assessment with [redacted] PD-L1 [redacted] assay used per manufacturer's instructions.

rr. Criterion amended per Amendment 7
rr1. Criterion amended per Amendment 8
rr2. Tumor demonstrates PD-L1 expression in ≥1% of tumor cells (TPS ≥1% or ≥1% TC) as assessed by IHC performed locally or by central laboratory testing (**refer to criterion 12.1.c2**).

Expansion Cohort 10 (NSCLC Activation/Maintenance Dosing): PD-1/L1 Inhibitor Pretreated (100 mg 1Q3W × 2 cycles; then 500 mg 1Q6W)

ss. Subjects with NSCLC who have received up to 4 prior systemic treatment regimens (maintenance treatment is considered being part of one treatment line) for metastatic disease with radiographic disease progression on or after last prior treatment.

tt. Subjects with NSCLC of any histology may be enrolled. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.

uu. Subjects should have received platinum-based therapy (or alternative chemotherapy due to platinum ineligibility, eg, a gemcitabine-containing regimen).

vv. Subjects must have received prior treatment with a PD-1/L1 inhibitor alone or in combination and must have radiographic disease progression on treatment. Sponsor approval is required for subjects with a BOR of SD or PD on a CPI containing regimen with a treatment duration of up to 16 weeks.

ww. Local results from the most recent PD-L1 test must be provided prior to enrollment. If local PD-L1 test results are unavailable, sponsor approval for enrollment is required.

xx. Criterion amended per Amendment 7
xx1. Subjects must have a PD-L1 expression result from the central laboratory available prior to C1D1 from a fresh tumor sample, which is obtained by core-needle biopsy and is taken after failure/stop of last prior treatment and prior to the first GEN1046 infusion.

yy. Tumor demonstrates PD-L1 expression in ≥1% of tumor cells (TPS ≥1%) as assessed by IHC determined by central laboratory testing.

Expansion Cohorts EC12 and EC13 (NSCLC Treatment-Naive for Metastatic Disease: GEN1046 in Combination with Pembrolizumab and Platinum-based Chemotherapy)

zz. Subjects with **non-squamous or squamous** metastatic NSCLC who have received no prior systemic treatment regimens for metastatic disease. Subjects must not have received prior treatment with a PD-1/L1 inhibitor.
Note:
- Prior adjuvant or neoadjuvant chemotherapy is permitted as long as the last administration of the prior regimen occurred at least 6 months prior to the start of the trial drug.
- Prior definitive chemoradiation for locally advanced disease is also permitted as long as the last administration of chemotherapy or radiotherapy (whichever was given last) occurred at least 6 months prior to the start of the trial drug.

aaa. Subjects with a histological or cytological diagnosis of non-squamous NSCLC must not have an EGFR-sensitizing mutation and/or ALK translocation/ROS1 rearrangement. EGFR-sensitizing mutations are those mutations that are amenable to treatment with an approved TKI. Documentation of EGFR and ALK status should be available per local assessment. If documentation of EGFR and ALK status is unavailable, sponsor medical monitor approval is required prior to enrollment.

bbb. If a local result from the most recent PD-L1 test exists, it must be provided prior to enrollment.

ccc. All subjects must provide a mandatory FFPE tumor sample that is obtained before C1D1 and originates from the metastatic stage of the cancer (**refer to inclusion criterion 12.1.e2**) for retrospective central biomarker evaluation. **The tumor tissue should ideally be from the same block of tumor used for local PD-L1 testing, if applicable.** Documentation of the tumor sample shipment (ie, airway bill) must be submitted to the sponsor prior to administration of the first dose of GEN1046. If it is not feasible to meet these requirements, the sponsor medical monitor's approval is required prior to enrollment.

For Both Dose Escalation and Expansion

3. Subject must be a man or woman ≥18 years of age.

4. Subject must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the trial and is willing to participate in the trial prior to any trial-related assessments or procedures. Where required by local or country-specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA and RNA). If a subject refuses to consent to DNA and RNA research in these specific regions, the subject is still eligible to participate in the trial.

5. Subject must have measurable disease according to RECIST 1.1.

6. Subject must have Eastern Cooperative Oncology Group (ECOG) 0-1.

7. Criterion amended as per Amendment 1
7.1 Subject must have organ and bone marrow function as follows:

a. Bone marrow/hematological function:
absolute neutrophil count (ANC) ≥1.5 × 10^9/L; hemoglobin ≥9.0 g/dL; platelet count ≥100 × 10^9/L

b. Liver function:

- Total bilirubin ≤ upper limit of normal (ULN)

- ALT ≤1.5 × ULN

- AST ≤1.5 × ULN

- Albumin ≥30 g/L

c. Coagulation status:

- Prothrombin time (PT)/international normalized ratio (INR) ≤1.5

- Activated partial thromboplastin time (aPTT) ≤1.5 × ULN (without anticoagulation therapy)

- Subjects receiving anticoagulant therapies should have the PT and aPTT within the therapeutic range of intended use of anticoagulants

d. Renal function:
Glomerular filtration rate (GFR) ≥45 mL/min/1.73 m² – eg, according to the abbreviated Modification of Diet in Renal Disease equation:

$$GFR = 186 \times (SCr^{-1.154}) \times (age^{-0.203})$$

where SCr, the serum creatinine level, is expressed in mg/dL; multiply it by 0.742 if the subject is female; multiply it by 1.212, if the subject is African-American (Levey et al., 1999).

8. A woman of reproductive potential must agree to use adequate contraception during and for 6 months after the last GEN1046 administration. Adequate contraception is defined as highly effective methods of contraception (please refer to Appendix 1 for more information). In countries where 2 highly effective methods of contraception are required this will be an inclusion criterion.

9. A woman (of childbearing potential) must have a negative serum (beta-human chorionic gonadotropin [beta-hCG]) at screening. Subjects that are postmenopausal or permanently sterilized (Appendix 1) can be considered as not having reproductive potential.

10. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the entire trial, until 6 months after last treatment.

11. Criterion amended as per Amendment 2.
11a. Criterion amended as per Amendment 1_US-1/IL-1.
11b. Criterion amended as per Amendment 1_EU-1.

11c. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control, eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, during and for 6 months after the last GEN1046 administration, and all men must also not donate sperm during the trial and for 6 months after receiving the last dose of GEN1046.

12. Criterion amended as per Amendment 5
12.1. Criterion amendment as per Amendment 2.

a. In the dose escalation part, all subjects must provide a tumor tissue sample (Formalin Fixed Paraffin Embedded blocks/slides) from archival tissue or fresh biopsy collected before Cycle 1 Day 1, preferably derived from advanced disease stage.

b. In the expansion part for cohorts with all-comers population EC1-EC7 and EC9: all subjects must provide a mandatory fresh biopsy (formalin fixed paraffin embedded [FFPE] blocks/slides) which contains tumor tissue and is taken after failure/stop of last prior treatment. Documentation of the fresh FFPE biopsy collection must be submitted to the sponsor as a part of the eligibility package prior to administration of first dose of GEN1046. Furthermore, the latest available archival tumor tissue sample, which is taken before failure/stop of last prior treatment, should be collected if available.

c. Criterion amended per Amendment 7

c1. In the expansion part for EC8: subjects must have a PD-L1 expression result (TPS ≥1% or ≥1% TC) available prior to C1D1 from a tumor sample from the metastatic stage of the cancer. Tumor PD-L1 expression can be determined by the sponsor-designated central laboratory CCI [redacted] or per site local assessment with CCI [redacted] PD-L1 CCI [redacted] assay used per manufacturer's instructions. In addition, all subjects must provide a FFPE tumor sample from the time metastatic disease was diagnosed. This should ideally be from the same block of tumor used for local PD-L1 testing, if applicable.

c2. In the expansion part for EC11: subjects must have a PD-L1 expression result (TPS ≥1% or ≥1% TC) available prior to C1D1 from a tumor sample from the metastatic stage of the cancer. Tumor PD-L1 expression can be determined by the sponsor-designated central laboratory CCI [redacted] or per site local assessment with CCI [redacted] PD-L1 CCI [redacted] assay used per manufacturer's instructions. In addition, all subjects should provide a FFPE tumor sample from the time metastatic disease was diagnosed. This should ideally be from the same block of tumor used for local PD-L1 testing, if applicable.

d. Criterion amended per Amendment 7

d1. In the expansion part for EC10: subjects must have a PD-L1 expression result (TPS ≥1%) from the central laboratory available prior to C1D1 from a fresh tumor sample which is obtained by core-needle biopsy (aspirates are not acceptable) and is taken after failure/stop of last prior treatment. Furthermore, the latest available archival tumor tissue sample, which has been taken before failure/stop of last prior treatment, should be collected if available.

e. Criterion amended per Amendment 7

e1. Criterion amended per Amendment 8

e2. All tumor samples for central biomarker evaluation (for all applicable cohorts) and tumor samples used for local PD-L1 testing (EC8 and EC11 only) must be of sufficient histological quality and have preserved tissue architecture (ie, core-needle biopsies, histological punctures, biopsies performed with mini-forceps, resections are accepted). The following samples are not acceptable for this trial: fine needle aspirates, cell blocks, cell pellets, clots, bone marrow or decalcified bone tissue, and any cytological specimens (smears, brushings, washings, lavages, and effusions). Tissue samples should not have been previously irradiated. FFPE tissue blocks are preferred to slides. In case it is not feasible to meet the tumor tissue requirements, the sponsor medical monitor's approval for enrollment is needed.

5.2 Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the trial.

1. Criterion amended as per Amendment 9.

1.1. Subject has uncontrolled intercurrent illness, including but not limited to:

a. Ongoing or active infection requiring IV treatment with anti-infective therapy that has been administered less than 2 weeks prior to first dose, or any ongoing systemic inflammatory condition requiring further diagnostic work-up or management during screening.

b. Symptomatic congestive heart failure (Grade III or IV as classified by the New York Heart Association), unstable angina pectoris, or cardiac arrhythmia.

c. Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg, despite optimal medical management.

d. Ongoing or recent (within 1 year) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for irAEs.

Note: The following conditions are not exclusionary: childhood asthma that has resolved, residual hypothyroidism that required only hormone replacement or psoriasis that does not require systemic treatment.

e. Subjects with a history of grade 3 or higher irAEs that led to treatment discontinuation of a prior immunotherapy treatment should be excluded. Subjects with irAEs below grade 3 that led to discontinuation should be discussed with the sponsor.

f. Subjects with a prior history of myositis, Guillain-Barré syndrome, or myasthenia gravis of any grade are excluded.

g. History of chronic liver disease or evidence of hepatic cirrhosis.

h. History of non-infectious pneumonitis that has required steroids or currently has pneumonitis.

i. History of organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of GEN1046.

j. Serious, non-healing wound, skin ulcer (of any grade), or bone fracture.

2. Criterion amended as per Amendment 4.
   2.1 Criterion amended as per Amendment 2.
   2.2 Criterion amended as per Amendment 1_US-1/IL-1.
   2.3 Criterion amended as per Amendment 1_EU-1.

   2.4 All subjects should undergo a computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain to document new or existing CNS lesions.

   a. Criterion amended as per Amendment 7

      a1. Any history of intracerebral arteriovenous malformation, cerebral aneurysm, spinal cord compression (from disease), carcinomatous meningitis, or stroke (within the last 6 months) will be excluded. Transient ischemic attack >1 month prior to screening is allowed.

   b. Criterion amended as per Amendment 7

      b1. Subjects with newly identified or known unstable or symptomatic CNS metastases will be excluded. Subjects with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression for at least 28 days from the radiological diagnosis of brain metastases by repeat imaging that should be performed during trial screening). Subjects should be clinically stable and should not be undergoing acute corticosteroid therapy or steroid taper or have received stereotactic radiation or whole-brain radiation within 14 days prior to C1D1. Chronic steroid therapy is acceptable provided that the dose is stable for the last 14 days prior to C1D1 (≤10 mg prednisone daily or equivalent). Note that radiotherapy is not allowed 14 days prior to first dosing and that the irradiated lesion cannot be used for efficacy assessment.

   c. Criterion removed as per Amendment 2.

3. Criterion amended as per Amendment 9.

3.1. Prior therapy:

a. Radiotherapy within 14 days prior to first GEN1046 administration or received lung radiation therapy of >30 Gy within 6 months of the first dose of trial treatment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. Note: Palliative radiotherapy will be allowed.
b. Unless otherwise noted below, treatment with an anti-cancer agent (within 28 days or after at least 5 half-lives of the drug, whichever is shorter), prior to GEN1046 administration. Accepted exceptions are bisphosphonates (eg, pamidronate, zoledronic acid, etc) and denosumab.

c. Subject has received any investigational agent (including investigational vaccines) or used an invasive investigational medical device within 28 days before the planned first dose of GEN1046 or is currently enrolled in an interventional trial.

   Note: Subjects who are in the follow-up phase of an interventional trial may participate if the subject has not received the investigational agent within 28 days of the first dose of GEN1046.

d. Prior treatment with live, attenuated vaccines within 3 weeks prior to initiation of GEN1046 treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Experimental and/or non-authorized SARS-CoV-2 vaccinations are not allowed.

e. Chronic systemic immunosuppressive corticosteroid doses, ie, prednisone >10 mg daily or a cumulative dose >150 mg prednisone within 14 days before the first GEN1046 administration. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is permitted.

f. Have received granulocyte colony stimulating factor (G-CSF) or granulocyte/macrophage colony stimulating factor (GM-CSF) support 4 weeks prior to first GEN1046 administration or being chronically transfusion dependent.

g. History of ≥ grade 3 allergic reactions to mAb therapy as well as known or suspected allergy or intolerance to any agent given in the course of this trial.

h. Subjects who discontinued treatment due to disease progression within the first 6 weeks of a CPI containing treatment.

i. Prior treatment with a 4-1BB (CD137) targeted agent.

j. Prior treatment with a T-cell agonist or anti-cytotoxic T lymphocyte-associated protein 4 targeted agent within 12 weeks prior to the initiation of treatment.

4. Toxicities from previous anti-cancer therapies that have not resolved to baseline levels or to grade 1 or less with the exception of alopecia, anorexia, vitiligo, fatigue, hyperthyroidism,

hypothyroidism, and peripheral neuropathy. Anorexia, hyperthyroidism, hypothyroidism, and peripheral neuropathy must have recovered to ≤ grade 2.

5. Known past or current malignancy other than inclusion diagnosis, except for:
    a. Cervical carcinoma of Stage 1B or less.
    b. Non-invasive basal cell or squamous cell skin carcinoma.
    c. Non-invasive, superficial bladder cancer.
    d. Prostate cancer with currently undetectable PSA.
    e. Breast cancer in BRCA1 or BRCA2 positive ovarian cancer subject (not applicable for breast cancer expansion cohort).
    f. Any curable cancer with a CR of >2 years duration.
6. Subject has known allergies, hypersensitivity, or intolerance to GEN1046 or its excipients.
7. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
8. Subject has had major surgery, (eg, requiring general anesthesia) within 4 weeks before screening, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the trial.

    Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate.

9. Known history of seropositivity for human immunodeficiency virus.
10. Known history/positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):
    a. Positive test for antibodies to hepatitis B core antigens

    and

    b. Negative test for antibodies to hepatitis B surface antigens.
11. Known medical history or ongoing hepatitis C infection that has not been cured.
12. Substance abuse, medical, psychological, or social conditions that may interfere with the subject's participation in the trial or evaluation of the trial result.
13. Subject has been dosed in this trial before.
14. Subject is a woman who is pregnant or breast-feeding.
15. EC9 only: Subject has contraindications to the use of docetaxel per local prescribing information.

16. Criterion amended as per Amendment 8.

    16.1 EC11A, EC11B, EC12, and EC13 only: Subject has contraindications to the use of pembrolizumab per local prescribing information.

17. CCI [redacted]

18. EC12 only: Subject has a known sensitivity to any component of cisplatin, carboplatin, or pemetrexed.

19. EC12 only: Subject is unable or unwilling to take folic acid or Vitamin B12 supplementation.

20. EC13 only: Subject has a known sensitivity to any component of carboplatin, paclitaxel, or nab-paclitaxel.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet the protocol-defined eligibility criteria (refer to Section 5.1 and Section 5.2). Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, subject withdrew consent, other reasons), and any serious adverse event (SAE) or AEs related to trial assessment.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once only (Note: No rescreening allowed if screen failure is due to negative PD-L1 result by central testing). The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised.

If rescreening is approved, complete new screening must be performed and all eligibility criteria must be reassessed. If more than 21 days have passed since the initial screening failed the subject must be re-consented. Also, a new ICF should be signed if updates have been made since signing of the first ICF.

Previously submitted CT and MRI scans are valid for rescreening purposes as long as the scanning acquisition date is ≤21 days prior to C1D1. Scans that exceed the 21-day window may be used for trial enrollment with sponsor approval. Blood samples taken during the previous screening process are also valid for rescreening purposes as long as they are fulfilling the initial timelines as indicated in Section 1.3, Table 1-2. If previously approved for eligibility, the same tumor biopsy sample is valid for rescreening purposes.

6 TREATMENT

6.1 Treatment Assignment

6.1.1 Subject Numbering

After signing the ICF, subjects will be given a screening number before they undergo any screening procedure. Subjects that meet the eligibility criteria and are enrolled will be assigned a subject number.

6.1.2 Treatment Assignment

This is an open-label trial; therefore, blinding of treatment will not be performed. Randomization will only be used for EC11A and EC11B in this trial.

For the dose escalation, site personnel must contact the contract research organization (CRO) when a potential subject has been identified in accordance with Section 4.1.1. If there is an opening in the currently enrolling dose level, the site will be given approval to start the screening process. If there is no opening, the subject will be placed on a waiting list and the site will be alerted of next available opening either in the currently enrolling dose level due to screening failures or at the next opened dose level.

In the expansion, an Interactive Response Technology system may be used to manage subject allocation to indication cohorts and to different doses and schedules, if applicable.

6.2 Dosage and Administration

In this trial, GEN1046, pembrolizumab, docetaxel, cisplatin, pemetrexed, carboplatin, paclitaxel, and nab-paclitaxel are considered IMP. Refer to Table 17-3 for EU authorization status for each IMP.

6.2.1 GEN1046

GEN1046 will be administered using IV infusion over a minimum of 60 minutes on Day 1 of each treatment cycle of either 21 days or 42 days after all procedures and assessments have been completed.

In the dose escalation part, subjects will be administered GEN1046 according to dose levels outlined in Section 4.1.1. In the expansion part, subjects will be administered the recommended flat dose of GEN1046 (100 mg 1Q3W) in Expansion Cohorts EC1 to EC7 and in EC9 (the docetaxel combination cohort; refer to Section 6.2.2 for instructions regarding docetaxel administration). Alternative doses/schedules may also be investigated. In EC 8 and EC10, subjects will receive 2 cycles of the activation dose (GEN1046 100 mg) administered 1Q3W followed by a higher maintenance dose (GEN1046 500 mg) administered 1Q6W from Cycle 3 onwards. In EC11 (the pembrolizumab combination cohorts), subjects will receive GEN1046 100 mg 1Q3W in combination with pembrolizumab 200 mg 1Q3W (11A) or GEN1046 100 mg 1Q6W in combination with pembrolizumab 400 mg 1Q6W (11B) (refer to Section 6.2.3 for instructions regarding pembrolizumab administration). In EC12, subjects will receive 4 cycles of GEN1046 in combination with pembrolizumab, pemetrexed, and cisplatin **OR** carboplatin

CCI [redacted]

CCI (refer to Table 1-1). In EC13, subjects will receive 4 cycles of GEN1046 in combination with pembrolizumab, carboplatin, and paclitaxel **OR** nab-paclitaxel CCI [redacted] (refer to Table 1-1).

As a routine precaution, subjects dosed with GEN1046 must be monitored during infusion and treated in an area with resuscitation equipment and emergency agents. All subjects must be observed during Cycle 1 and Cycle 2 on Day 1 for at least 4 hours after ending infusion of GEN1046. For all subsequent cycles, subjects must be observed for at least 2 hours after ending infusion of GEN1046.

Please refer to the investigational medicinal product (IMP) Manual for additional information regarding GEN1046 administration.

6.2.2 Docetaxel

Docetaxel will be administered according to the locally approved label.

Docetaxel will be administered in combination with GEN1046 using IV infusion on Day 1 of each 3-week treatment cycle (until disease progression or until one of the predefined discontinuation of treatment criteria has been met.). GEN1046 is to be administered first. The docetaxel infusion should begin at least 30 minutes after the completion of the GEN1046 infusion. Refer to Section 6.2.1 for instructions regarding GEN1046 administration. Docetaxel will be administered at a dose of 55 mg/m^2 or 75 mg/m^2, depending on the number of prior DLTs observed. The maximum tested dose of docetaxel will be 75 mg/m^2.

Vital signs will be collected for docetaxel infusions according to Section 9.4.2. For further details, see the local prescribing information for docetaxel. All subjects assigned to receive docetaxel should be premedicated with corticosteroids according to local practice (eg, oral dexamethasone at 16 mg per day [8 mg twice daily] for 3 days, starting a day prior to administration) to reduce the incidence and severity of fluid retention, as well as the severity of hypersensitivity reactions.

Antiemetic prophylaxis may be administered at the treating physician's discretion according to local practice.

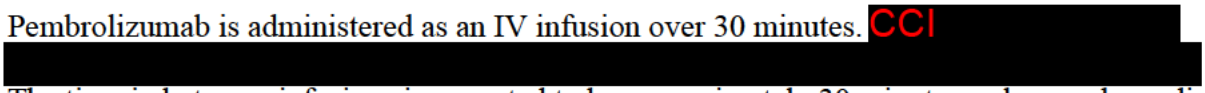
6.2.3 Pembrolizumab

Pembrolizumab 200 mg 1Q3W will be administered for up to 35 cycles and pembrolizumab 400 mg 1Q6W will be administered for up to 18 cycles, for a total of up to 2 years.

EC11A and EC11B: Pembrolizumab 200 mg or 400 mg or will be administered on Day 1 of each 3-week OR 6-week treatment cycle, respectively, depending on the randomization, after all pretreatment procedures and assessments have been completed. CCI [redacted]

EC12 and EC13: Pembrolizumab 200 mg will be administered on Day 1 of each 3-week treatment cycle, after all pretreatment procedures and assessments have been completed, as follows.

Pembrolizumab is administered as an IV infusion over 30 minutes.



The time in between infusions is expected to be approximately 30 minutes or longer depending on the situation. Dose reductions for pembrolizumab are not recommended.

6.2.4 Cisplatin/Carboplatin

Treatment of cisplatin or carboplatin will be prepared and administered as per the IMP Manual. The body surface area in m^2 should be calculated per local guidance.

Cisplatin OR carboplatin will be administered on Day 1 of the first 4 treatment cycles after completion of all procedures and assessments according to Section 6.2.3.

Cisplatin is given as a dose of 75 mg/m^2 as an IV infusion using an infusion duration according to local practice and it should be immediately preceded and followed by hydration procedures and administered according to the IMP Manual.

Carboplatin will be administered using IV infusion at the protocol-specified dosage of AUC 5 mg/mL/min (EC12) or AUC 6 mg/mL/min (EC13). The calculated dosage for carboplatin will be based upon a subject's GFR in mL/min and target AUC in mg × min/mL by the Calvert Formula. GFR may be estimated by calculated creatinine clearance (CrCl) or based upon local institutional standards. Refer to the carboplatin package insert for instructions regarding the preparation of carboplatin and administration of infusion solution. Subjects who experience CTCAE ≥ grade 2 renal toxicity (serum creatinine >1.5 × ULN) require recalculation of the carboplatin dose for subsequent cycles. Subjects should receive premedication for carboplatin per institutional SOC.

Calvert Formula:

Total Dose (mg) = (target AUC) × CrCl+25).

The estimated GFR used in the Calvert Formula should not exceed 125 mL/min and the maximum carboplatin dose is 750 mg. Alterations in renal function may require a recalculation of the carboplatin dose (Section 7.3).

6.2.5 Pemetrexed

Pemetrexed will be administered as an IV infusion over 10 minutes 1Q3W. It is also recommended to administer dexamethasone prophylaxis 4 mg, orally twice per day (or equivalent) taken the day before, day of, and day after pemetrexed administration (refer to Section 6.4.2.1 for further details related to the potential impact on immunotherapy).

Pemetrexed will be prepared and administered as per IMP Manual at the dose of 500 mg/m^2. All subjects should receive the appropriate supplementation of Vitamin B12 and folic acid as listed below:

- Folic Acid 350 to 1000 µg oral: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent Vitamin B12 injections may be given the same day as pemetrexed administration.

6.2.6 Paclitaxel

Paclitaxel 200 mg/m^2 will be administered as an IV infusion over 3 hours 1Q3W for 4 cycles as per IMP Manual. All subjects should be premedicated with oral or IV steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice. Paclitaxel should be completely administered before initiating the carboplatin dose.

6.2.7 Nab-paclitaxel

Nab-paclitaxel will be administered for 4 cycles by IV infusion at a dose of 100 mg/m^2 over 30 to 40 minutes as per IMP Manual. Subjects will be dosed on Days 1, 8, and 15 of each 1Q3W cycle (1Q1W). Nab-paclitaxel should be completely administered before initiating the carboplatin dose.

6.3 Treatment Compliance

Trial treatment will be administered by site personnel to assure compliance with trial requirements.

6.4 Concomitant Medications and Therapies

6.4.1 Permitted Concomitant Medications and Therapies

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “prohibited” (Section 6.4.2). Administration of concomitant medications must be reported in the appropriate section of the electronic case report form (eCRF).

The following concomitant medication and therapies are permitted during the trial:

- Palliative radiotherapy during the trial will be allowed for local pain control provided that:
  - In the opinion of the investigator, (i) the subject does not have PD AND (ii) no more than 10% of the subject’s bone marrow is irradiated AND (iii) the radiation field does not encompass a target lesion.

- Radiation therapy to a symptomatic solitary non-target lesion or to the brain may be allowed at the investigator’s discretion.

- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator’s discretion. For EC9 (GEN1046 – docetaxel combination), administration of prophylactic G-CSF or pegylated G-CSF is recommended with every cycle in order to prevent febrile

neutropenia and prolonged severe neutropenia. Subjects are permitted to be taking chronic erythropoietin provided that no dose adjustment was made within 2 months before the first dose of GEN1046.

- Prophylactic antibiotics are also permitted per institutional standard practice.
- Blood cell transfusion is allowed if clinically indicated.
- Steroid treatment is permitted as reactive premedication to GEN1046 and to modulate symptoms of an irAE (refer to Section 7.3.1.1). Steroids can also be given as prophylaxis to subjects receiving chemotherapy per the local standard of care (Section 6.4.2.1). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is also allowed (Section 6.4.2).
- Bisphosphonates (eg, pamidronate, zoledronic acid, etc.) and denosumab.
- Multivitamins, vitamin D, calcium, and supplements in prevention of weight loss.
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is generally permitted, including mRNA-based, protein-based, or nonreplicating viral vector-based vaccines. Please consider choosing an appropriate type of SARS-CoV-2 vaccine and consult with an infectious disease expert if desired. Please note, SARS-CoV-2 vaccine should neither be administered during the DLT observation period in dose escalation parts including EC9 nor during the EC11A and EC11B safety run-in (GEN1046 in combination with pembrolizumab) nor during the EC12 and EC13 safety run-in (GEN1046 in combination with pembrolizumab and platinum-based chemotherapy doublets).

6.4.2 Prohibited Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial intervention or vaccination may be required. The investigator is to discuss prohibited medication/vaccination with the sponsor's medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial treatment requires the mutual agreement of the investigator, the sponsor, and the subject.

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications and substances are prohibited during the trial:

- Any other investigational therapy.
- Anti-neoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- Immunotherapy not specified in the protocol.

- Chronic systemic immunosuppressive corticosteroid doses (ie, prednisone >10 mg daily) or steroid treatment for any other purpose than to manage emergency situations (according to institutional standards), chemotherapy prophylaxis (Section 6.4.2.1), reactive premedication to GEN1046 or corticosteroids to modulate symptoms of an irAE (Section 7.3.1.1).

- Live attenuated vaccines while participating in the trial and for 3 months following the last dose of GEN1046. Note: Seasonal influenza vaccines are generally killed virus vaccines and are permitted; however, intranasal influenza vaccines are live attenuated and are not allowed.

- No dietary supplements are allowed during the trial period (except for vitamins, calcium, and supplements in prevention of weight loss). The administration of non-approved, herbal and/or natural remedies used to prevent or treat disease and symptoms should be avoided with the exception of senna that can be used as required.

The following additional restrictions are valid for subjects receiving pembrolizumab or docetaxel or paclitaxel in combination with GEN1046:

- Docetaxel is a cytochrome P450 (CYP) 3A4 substrate. Avoid using concomitant strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole). There are no clinical data with a dose adjustment in patients receiving strong CYP3A4 inhibitors.
- In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was co-administered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. If a subject receives any of these during the trial, the sponsor must be notified for evaluation of whether the subject can continue treatment or not.
- The metabolism of paclitaxel is catalyzed, in part, by CYP2C8 and CYP3A4. Therefore, caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (eg, rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

For cisplatin and carboplatin, concurrent therapy with nephrotoxic or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin, and diuretics, may increase or exacerbate toxicity.

No formal drug interaction studies have been performed with pembrolizumab.

*6.4.2.1 **Premedication and Antiemetics for Subjects Receiving Combination Therapy***

Prophylactic premedication for the administration of GEN1046 or pembrolizumab is not required. For reactive premedication to GEN1046, please refer to Section 7.3.1.1 and Table 7-1. For the management of IRR, please refer to Section 7.3.1.5.

Antiemetic therapy should follow local standards or American Society of Clinical Oncology guidelines. In general, corticosteroid antiemetic premedication should be avoided for 3 days prior to and 30 days after GEN1046 therapy. Nab-paclitaxel is associated with a low emetic

potential risk whereas cisplatin and carboplatin AUC ≥4 bear high emetic risk. Cisplatin is more emetogenic than carboplatin. If dexamethasone is to be given, consider limiting the initial use to no more than 8 mg on Day 1 of the trial treatment. The need for additional dexamethasone should be discussed with the sponsor. If emesis is not controlled, switching from cisplatin to carboplatin should be considered.

Premedication for the administration of paclitaxel is required. All subjects treated with paclitaxel should be premedicated with steroid and antihistamines.

All subjects treated with pemetrexed should be premedicated with folic acid and Vitamin B12 according to the approved product label and/or standard practice. To reduce the incidence and severity of skin reactions, a corticosteroid should be given the day prior to, on the day of, and the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day (see Section 6.2.5).

6.5 Trial Drug Information

6.5.1 GEN1046

6.5.1.1 Physical Description

GEN1046 – 20 mg/mL formulated in CCI – is a CCI solution supplied as a concentrate for solution for infusion to be diluted (at site) in 0.9% NaCl (saline).

6.5.1.2 Packaging

GEN1046 will be provided in a CCI glass vial containing CCI of GEN1046 CCI.

6.5.2 Pembrolizumab

6.5.2.1 Physical Description

Pembrolizumab (Keytruda®) infusion is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion.

6.5.2.2 Packaging

Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, US Pharmacopeia (USP).

6.5.3 Cisplatin

6.5.3.1 Physical Description

Cisplatin is a clear to opalescent, colorless to slightly yellow solution supplied as a concentrate for solution for infusion to be diluted (at site).

6.5.3.2 Packaging

Cisplatin will be supplied as 1 mg/mL.

6.5.4 Carboplatin

6.5.4.1 Physical Description

Carboplatin is a clear colorless solution supplied as a concentrate for solution for infusion to be diluted (at site).

6.5.4.2 Packaging

Carboplatin will be supplied as 10 mg/mL.

6.5.5 Pemetrexed

6.5.5.1 Physical Description

Pemetrexed will be either a white to off-white lyophilized powder (or solid) for concentrate for solution for infusion or a concentrate for solution for infusion. After reconstitution of powder, each vial contains 25 mg/mL of pemetrexed.

6.5.5.2 Packaging

Pemetrexed will be supplied as 25 mg/mL.

6.5.6 Paclitaxel

6.5.6.1 Physical Description

Paclitaxel is a clear colorless to slightly opalescent viscous solution supplied as a concentrate for solution for infusion to be diluted (at site).

6.5.6.2 Packaging

Paclitaxel will be supplied as 6 mg/mL.

6.5.7 Nab-paclitaxel

6.5.7.1 Physical Description

Nab-paclitaxel is a white to yellow powder for dispersion for infusion to be reconstituted and diluted (at site).

6.5.7.2 Packaging

Nab-paclitaxel will be supplied as 5 mg/mL powder for dispersion for infusion.

6.5.8 Docetaxel

Refer to the local label for the docetaxel drug description and packaging information.

6.5.9 Preparation, Handling, and Storage

Refer to the IMP Manual for additional guidance on trial drug preparation, handling, and storage.

6.5.10 Labeling

Trial drug labels will contain information to meet the applicable regulatory requirements.

6.5.11 Drug Accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of trial drugs in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the trial.

At trial close-out, and as appropriate during the course of the trial, the investigator will destroy all used and unused trial drug, packaging, drug labels. A copy of the completed drug accountability log should be provided to the monitor or to the address provided in the investigator folder at each site (unless otherwise agreed with sponsor).

6.6 Technical Complaint Handling

A technical complaint is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A technical complaint may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of technical complaint information from trials are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of technical complaint information; all trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

6.6.1 Procedures

All initial technical complaints must be reported to the sponsor by the trial-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an AE, the trial-site personnel must report the AE to the sponsor according to the AE and SAE reporting process and timelines (Section 10.5) in addition to reporting the technical complaint. A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.6.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding technical complaint issues are listed on the contact information page(s), which will be provided as a separate document.

7 DOSE MODIFICATIONS AND SAFETY MANAGEMENT GUIDELINES

7.1 Dose-limiting Toxicity

For the purpose of dose escalation or safety run-in evaluations, the DLT monitoring period will be 21 days. The occurrence of any of the toxicities outlined in this section will be considered a DLT if assessed by the investigator to be at least possibly related to GEN1046. Toxicities clearly not related to GEN1046 (eg, disease progression, comorbidity, etc) will not be considered a DLT. SAEs, non-serious ≥ grade 3 AEs and clinically significant abnormal lab values ≥ grade 3 **at least possibly related** to GEN1046 will be collected and assessed for DLTs (for each dose level during the first cycle). CTCAE v5.0 will be used to grade the intensity of AEs, with the exception of CRS, which will be graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria described by (Lee et al., 2019).

DLT criteria are defined below:

- Grade 5 toxicity.

Hematological

- Grade 4 neutropenia (ie, ANC <0.5 × 10^9 cells/L) lasting more than 7 days.
- Grade 3 and 4 febrile neutropenia (ie, ANC <1.0 × 10^9 cells/L with a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour).
- Grade 4 thrombocytopenia (≤25.0 × 10^9 platelets/L) for minimal duration of 7 days.
- Grade 3 and 4 hemorrhage associated with thrombocytopenia of ≥ grade 3 requiring platelet transfusion.
- Grade 4 anemia.

Non-Hematological

- Liver toxicity (transaminases and bilirubin elevations).

  Evaluation as to whether the elevation qualifies as a DLT is based on the individual subject's baseline levels as follows:

Transaminases at Baseline	Bilirubin at Baseline	Transaminases [a] on Treatment		Bilirubin [a] on Treatment	DLT
≤ ULN	≤ ULN	>3 – 5 × ULN	or	>1.5 – 3 × ULN	if not recovered [b]
≤1.5 × ULN	≤ ULN	>5 × ULN	or	>3 × ULN	in any case

DLT=dose-limiting toxicity; ULN=upper limit of normal.
a Any transaminase (alanine aminotransferase or aspartate aminotransferase) and/or bilirubin ≥ grade 2 elevation needs to be checked 2x/week for up to 4 weeks.
b Must recover to <3 × ULN for transaminases and to <1.5 × ULN for bilirubin within 14 days. For continuing dosing see Section 7.3.

- Grade 3 nausea that does not respond to optimal antiemetic treatment within 7 days.
- Grade ≥3 vomiting that does not respond to optimal antiemetic treatment within 3 days.
- Grade ≥3 diarrhea that does not respond to optimal antidiarrheal treatment within 3 days.
- Grade 3 irAEs that do not improve to ≤ grade 1 within 7 days by appropriate care or with corticosteroids **except for**:
  - Grade 3 pneumonitis which always qualifies as a DLT.

  - Grade 3 nephritis (defined as inflammation of the kidney affecting the structure associated with grade 3 creatinine increase) which always qualifies as a DLT.
- Any grade 4 irAE.

- Any other ≥ grade 3 non-hematological AE (including liver toxicities other than increases of transaminases and bilirubin), which occurs during the first GEN1046 treatment cycle ***excluding***:
  - Grade 3 CRS, which has improved to grade 1 or resolved within 48 hours.
  - Grade 3 fever (>40.0°C for ≤24 hours).
  - Grade 3 hypotension (resolving within 24 hours).
  - Grade 3 IRRs that resolve to ≤ grade 1 within 24 hours.
  - Non-hematological laboratory abnormalities that have no clinical consequence and resolve to ≤ grade 2 within 7 days (this also includes electrolyte abnormalities that respond to medical intervention).
  - Grade 3 fatigue when fatigue was present at baseline or that lasts for <14 days after the last administration of GEN1046.
  - Grade 3 anorexia when grade 2 anorexia was present at baseline or that lasts for <1 day after the last administration of GEN1046.

Dose Escalation:
- Subjects experiencing a DLT (an AE fulfilling the DLT criteria within the DLT period of 21 days) should discontinue trial drug immediately. If requested by the investigator, the sponsor may allow a subject with a DLT to continue in the trial considering a reduced dose. For this decision, a thorough benefit-risk assessment of the individual subject is required and consultation of the DMC needs to be considered.

7.2 Dosing Modification Guidance and Safety Stopping Criteria

Decisions regarding dose modification of trial drug should be made using clinical judgment, taking into account relatedness of the AE to the trial drug and the subject's underlying condition.

GEN1046 (and pembrolizumab, [EC11A, EC11B, EC12, and EC13 only]) are considered immune modulators and AEs associated with these compounds may have an immunologic etiology (ie, irAEs) which may be defined as an AE consistent with an immune phenomenon associated with drug exposure after all other etiologies have been eliminated.

IrAEs may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of treatment, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue trial treatment and administer

corticosteroids. Dosing modifications for irAEs including transaminase (ALT and AST) and bilirubin increases are outlined in Section 7.3 and should be managed according to Table 7-1.

If a subject experiences neutropenia or febrile neutropenia considered related to GEN1046, dose modification and supportive care guidance is provided in Table 7-2. For all other AEs considered related to GEN1046 treatment, general instructions for interruption and restarting of trial treatment are outlined in Table 7-3. AEs with clear alternative causality may be exempt from dose modification rules.

GEN1046 or GEN1046 combination regimens must be permanently discontinued in case of a dose delay of more than 21 days due to toxicity possibly related to GEN1046 or the combination regimen unless otherwise approved by the sponsor medical monitor. No intra-subject dose de-escalation will be allowed.

7.3 Dosing Modification for Specific Adverse Events

7.3.1 GEN1046 and GEN1046 plus Pembrolizumab

7.3.1.1 Immune-Related Adverse Events (irAEs)

Immune CPIs are associated with a spectrum of adverse effects related to the immune-mediated MoA and are different from other systemic therapies such as cytotoxic chemotherapy (Brahmer et al., 2018; Schneider et al., 2021). Guidance for dose modification and management of irAEs is provided in Table 7-1. For additional guidance on the recommended management of irAEs, please refer to the *Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline* (Brahmer et al., 2018; Schneider et al., 2021).

<u>General Guidance</u>

Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. CCI [redacted]

- Based on the severity of irAEs, trial treatment should be withheld or permanently discontinued and corticosteroids administered.
- For severe and life-threatening irAEs, IV corticosteroid should be initiated first (under hospital admission). Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.
- It is important to exclude infections diligently at admission and to keep monitoring subject closely (eg, with vital signs, hematology, LFTs, procalcitonin, and inflammatory markers, including CRP and ferritin) on a daily basis to exclude potential new infections. Infections should be treated immediately and adequately per the local standard of care. For infections ongoing at the time of dosing, consider dose delay until resolution.
- If subject is receiving high-dose corticosteroids (eg, ≥2 mg/kg for ≥3 days), initiate broad-spectrum antibiotics covering nosocomial infections as well as antifungals (unless there are

contraindications) due to the increased risk of infections during immunosuppression. Concurrent neutropenia may increase the risk of infection.

- Corticosteroid taper should be initiated for corticosteroid treatment doses of 0.5 mg/kg or higher upon irAE improving to grade 1 or less and continue to taper over at least 4 weeks.
- CCI [redacted]
- CCI [redacted]
- For grade 1 irAEs, trial treatment should be continued with close monitoring unless otherwise noted in Table 7-1.
- For > grade 1 irAEs, withhold treatment until resolution to ≤ grade 1 unless otherwise specified.
- Permanent discontinuation of trial treatment is always recommended with grade 4 toxicities with the exception of endocrinopathies that have been controlled by hormone replacement or if otherwise specified in Table 7-1.
- Trial treatment should also be permanently discontinued for any serious grade 3 irAE that recurs and for any life-threatening irAE.
- For a description and guidance for management of hyperinflammatory syndromes, please refer to Section 7.3.1.3.

Table 7-1 Dosing Modification and Management of Immune-Related Adverse Events

Immune-Related AEs	Toxicity Grade	Dose Modification	Guidance for Management of irAEs
Pneumonitis	Grade 1 or Grade 2	1st occurrence If there is radiographic evidence of pneumonitis, withhold treatment until resolution to ≤ grade 1 and corticosteroid has been tapered[1] 2nd occurrence Permanently discontinue	Monitor for signs and symptoms of pneumonitis. Evaluate for pneumonitis with radiographic imaging. For ≥ grade 2: Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone* or equivalent) followed by taper. Add prophylactic antibiotics.
	Grade 3 or Grade 4	Permanently discontinue	
Colitis	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of colitis. Consider gastroenterology consultation and confirm diagnosis of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone* or equivalent) followed by taper.
	Grade 3	Withhold treatment until resolution to ≤ grade 1 and corticosteroid has been tapered[1]	
	Grade 4	Permanently discontinue	

Immune-Related AEs	Toxicity Grade	Dose Modification	Guidance for Management of irAEs
CCI			

Immune-Related AEs	Toxicity Grade	Dose Modification	Guidance for Management of irAEs
	Grade 4	Permanently discontinue	CCI [redacted]
T1DM or Hyperglycemia	Newly diagnosed T1DM or Grade 3-Grade 4 hyperglycemia	Withhold until glucose control is obtained[2,3]	Monitor for hyperglycemia or other signs and symptoms of diabetes. Consider endocrinology consultation. Consider administration of insulin for type 1 diabetes. Consider administration of anti-hyperglycemic in subjects with hyperglycemia.
Hypophysitis	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of hypophysitis. Consider endocrinology consultation. Consider administration of corticosteroids and initiate hormonal replacements as clinically indicated. Corticosteroid taper should be initiated upon irAE improving to grade 1 or less.
	Grade 3 or Grade 4	Withhold until subject is stabilized on replacement therapy or permanently discontinue[2]	
Hypothyroidism	Grade 2	Continue treatment at the discretion of the investigator	Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic subjects with any degree of TSH elevation or in asymptomatic subjects with TSH levels that persist >10 mIU/L (measured 4 weeks apart).
	Grade 3-Grade 4	Withhold until symptoms resolve to baseline with appropriate supplementation[7]	
Hyperthyroidism	Grade 2	Continue treatment at the discretion of the investigator	Monitor for signs and symptoms of thyroid disorders. Consider management with thionamides and beta-blockers as appropriate.
	Grade 3-Grade 4	Withhold until symptoms resolve to baseline with appropriate therapy consultation or permanently discontinue[2,3]	
Nephritis and renal dysfunction	Grade 1	Consider temporary hold pending consideration of baseline renal function and to confirm etiology[1]	Monitor for changes in creatinine levels. For ≥ grade 2: If worsening or no improvement, consider administration of corticosteroids (prednisone* 1 to 2 mg/kg or equivalent) followed by taper. Corticosteroid taper should be initiated upon irAE improving to grade 1 or less.
	Grade 2	Withhold treatment until resolved to baseline[1]	
	Grade 3-Grade 4	Permanently discontinue	

Immune-Related AEs	Toxicity Grade	Dose Modification	Guidance for Management of irAEs
Skin toxicities	Grade 1 or Grade 2	Continue treatment at the discretion of the investigator	Based on the severity of the skin toxicity, consider administration of corticosteroids. Corticosteroid taper should be initiated upon irAE improving to grade 1 or less. For signs or symptoms of SJS or TEN, withhold and refer the subjects for specialized care. If SJS or TEN is confirmed, permanently discontinue.
	Grade 3	Withhold treatment until resolved to ≤ grade 1[1]	
	Grade 4	Permanently discontinue	
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	Based on severity of the AE, consider administration of corticosteroids. Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 2, 3, or 4	Permanently discontinue	
All other irAEs[4, 5, 6]	Grade 2	Continue treatment at the discretion of the investigator	Based on type and severity of AE, consider administration of corticosteroids. Permanently discontinue for any grade 3 irAE that recurs and for any life-threatening irAEs.
	Grade 3	Withhold or permanently discontinue[2]	
	Grade 4	Permanently discontinue	

*=not approved in Japan; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; irAE=immune-related adverse event; SJS=Stevens-Johnson syndrome; T1DM=type 1 diabetes mellitus; TEN=toxic epidermal necrolysis; TSH=thyroid stimulating hormone.

1 The next dose of GEN1046 can maximally be delayed 21 days unless approved otherwise by the sponsor medical monitor. If irAE resolves within 21 days to baseline, restart treatment at the same dose level after consulting the sponsor medical monitor.
2 Investigator must contact the sponsor to discuss whether the subject should be withdrawn from GEN1046 treatment or if the next dose should be delayed. Subjects may be treated on the same dose and schedule. The sponsor may also consult the DEC as specified in Section 10.10.
3 For subjects with Grade 3 or 4 immune-related endocrinopathy leading to withholding of GEN1046 dosing, treatment may be resumed when the AE recovers to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).
4 For EC11A, EC11B, EC12, and EC13: For irAEs specifically associated with anti-PD-1-treatment, please refer to local prescribing information for pembrolizumab.
5 Refer to Section 7.3.1.3 for guidance regarding hyperinflammatory syndromes (hemophagocytic lymphohistiocytosis [HLH] and cytokine release syndrome [CRS]).
6 Refer to (Schneider et al., 2021) reference for guidance on immune-related musculoskeletal, nervous system, hematologic, cardiovascular, ocular, and specific cutaneous toxicities.
7 The decision to withhold or permanently discontinue GEN1046 or GEN1046 combination regimen is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, GEN1046 or GEN1046 combination regimen may be resumed.

7.3.1.2 Neutropenia and Febrile Neutropenia

Table 7-2 Dose Modification and Management of Neutropenia and Febrile Neutropenia

CTCAE Term	Toxicity Grade (CTCAE v5.0)	Dose Modification	Guidance for Management of AE
Neutropenia or Febrile neutropenia	Grade 3 or Grade 4	Withhold treatment until resolution to ≤ grade 1	Administer colony stimulating factors including G-CSF, pegylated G-CSF or GM-CSF according to Institutional standards. For grade 3 or 4 neutropenia occurring in Cycle 1, grade 3 or 4 neutrophil count must be observed in 2 consecutive assessments at least 12 hours apart without improvement prior to administration of growth factors. For Expansion Cohort EC9 (GEN1046 – docetaxel combination), administration of prophylactic G-CSF or pegylated G-CSF is recommended with every cycle in order to prevent febrile neutropenia and prolonged severe neutropenia.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; G-CSF=granulocyte colony stimulating factor; GM-CSF=granulocyte/macrophage colony stimulating factor.

7.3.1.3 Hyperinflammatory Syndromes

These include rare but potentially fatal irAEs syndromes of immune hyperactivation caused by cytokine release and a resulting systemic inflammatory response, like in CRS and HLH.

7.3.1.3.1 Cytokine Release Syndrome

Any event of CRS should be graded according to ASTCT criteria described by (Lee et al., 2019).

Trial treatment should be permanently discontinued for subjects with grade ≥3 CRS (except for grade 3 CRS which has improved to grade 1 or resolved within 48 hours). However, per protocol, subjects should continue safety follow-up until the subject withdraws from the trial or starts another course of systemic anti-cancer therapy.

Management of CRS should follow the established guideline (Varadarajan et al., 2020) or local SOC, with supportive treatment controlling fever, hypotension, and hypoxia; and in more severe cases, with anti-IL-6R mAb (eg, tocilizumab), systemic steroids, and vasopressors.

7.3.1.3.2 Hemophagocytic Lymphohistiocytosis

HLH is an hyperinflammatory hyperferritinemic immune response syndrome driven by T cells and associated with a cytokine storm. Acquired, secondary HLH is the most common subtype in adults. HLH triggers include occult malignancy (mainly lymphoma), infections, and iatrogenic causes like immunotherapy with immune CPIs (La Rosée et al., 2019).

Hyperferritinemia should always prompt inclusion of HLH as differential diagnosis. If ferritin levels are increased above 500 µg/L, they should be monitored closely. Ferritin values characteristic of HLH in adults are often >7000 µg/L. However, any rapid increase in the ferritin level compared to baseline per clinical assessment should raise the index of suspicion (Hines et al., 2023). If HLH is suspected, elevated soluble IL-2 receptor (sCD25) has been reported as a diagnostic test for adult HLH and it is recommended to assess sCD25 locally (per local standard)

together with fibrinogen, triglycerides, and D-dimer. Other features supporting an HLH diagnosis that are not part of the HLH-2004 criteria below include elevated liver transaminases, hyperbilirubinemia, hepatomegaly and elevated LDH (La Rosée et al., 2019).

The HLH-2004 diagnostic criteria can be a useful tool for assessing HLH diagnosis. According to this score, the diagnosis of HLH can be established if 5 of the following 8 criteria are fulfilled:

1. Fever
2. Splenomegaly
3. Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood):
   a. Hemoglobin <90 g/L
   b. Platelets $<100 \times 10^9$ /L
   c. Neutrophils $<1.0 \times 10^9$ /L
4. Hypertriglyceridemia and/or hypofibrinogenemia:
   a. Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL)
   b. Fibrinogen ≤1.5 g/L
5. Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy
6. Low or no NK cell activity (according to local laboratory reference)
7. Ferritin ≥500 µg/L
8. sCD25 (ie, soluble IL-2 receptor) ≥2400 U/mL

The diagnosis of HLH can also be established if a molecular diagnosis consistent with HLH is fulfilled.

There may be overlapping features in the pathophysiology and presentation between hyperinflammatory syndromes. Furthermore, the HLH-2004 diagnostic criteria above were derived from children with primary HLH. Based on experience from the acasunlimab development program and similarities with the safety profile of CAR T-cell therapies, it is recognized that pathology and hyperinflammatory processes observed with acasunlimab are distinct from primary HLH and more like immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (Hines et al., 2023). **It is therefore recommended to start treatment solely on a strong suspicion of "HLH-like syndrome," even if 5 of the 8 HLH-2004 diagnostic criteria are not met.**

The management of HLH should be tailored to control hyperinflammation and to treat identified disease triggers.

Treatment with high-dose corticosteroids (start dose 2 mg/kg IV) is the cornerstone of treatment. Early intervention with high-dose steroids alone may be successful in the treatment of HLH induced by immune checkpoint blockade (Sadaat and Jang, 2018; Takahashi et al., 2020) . If no reversal of laboratory parameters (including ferritin and bilirubin increases) within 24 hours, pulsed corticosteroids, eg, 1000 mg/day for 3 days according to (Takahashi et al., 2020), should be initiated immediately. If no improvement within 24 to 48 hours from the initiation of corticosteroid pulse therapy, treatment with anakinra or JAK1/2 inhibitors should be added (Hines et al., 2023; Keenan et al., 2021). For refractory cases, etoposide (an element of the HLH-94 protocol) may be used. Dose and frequency adjustments are advised for adult patients (La Rosée et al., 2019).

CCI

- CCI
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7.3.1.4 Other Immune-Related AEs

Table 7-3 General Dose Modification Recommendations and Management of Other Immune-Related AEs Not Specifically Mentioned in Section 7.3

CTCAE Grade/Severity	Hold Treatment (Y/N)	Timing for Restarting Treatment
Grade 1 or Grade 2	N	Continue treatment at the discretion of the investigator.
Grade 3 (Severe)	Y	Withhold treatment until resolution to ≤ grade 1 or baseline.
Grade 4 (Life-Threatening)	Y	Permanent discontinuation except if approved by medical monitor. If continuing on treatment, toxicity must resolve to Grade 1 or baseline.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; N=no; Y=yes.

7.3.1.5 Infusion-Related Reactions to GEN1046

The following treatment guidelines are provided below for subjects who experience an IRR associated with administration of GEN1046.

- Grade 1: If an IRR grade 1 occurs, the infusion does not need to be interrupted and can be continued at the investigator's discretion at half the infusion rate under close medical supervision.
- Grade 2-3: If an IRR grade 2 or 3 occurs, the infusion should be interrupted and appropriate medical management instituted. The infusion may be re-started at the investigator's discretion at half the infusion rate under close medical supervision if symptoms have resolved to ≤ grade 1 within an hour.
  - Subjects who have experienced prior infusion-related grade 2 or 3 reactions in the trial should be premedicated. Premedication to prevent IRR in subsequent infusions may be

administered at the investigator's discretion according to local guidelines but preferably includes an antihistamine (eg, diphenhydramine 50 mg or equivalent antihistamine), acetaminophen/paracetamol (eg, acetaminophen 500-1000 mg or equivalent), and if considered necessary, subjects should receive corticosteroids at a suggested maximum dose of 100 mg prednisone or equivalent.
    - If the subject has a second grade 3 IRR despite premedication, the infusion should be stopped and the subject should be withdrawn from treatment.
- Grade 4: If anaphylaxis or grade 4 IRR occurs, administration of GEN1046 should be discontinued immediately and permanently and appropriate medical therapy should be administered.

Please note:

- As a routine precaution, all subjects must be observed during Cycle 1 and Cycle 2 on Day 1 for at least 4 hours after ending infusion of GEN1046. For all subsequent cycles, subjects must be observed for at least 2 hours after ending infusion of GEN1046.
- Subjects must be observed in an area with resuscitation equipment and emergency agents.
- At all times during GEN1046 infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.
- All premedication must be reported on the concomitant medication page in the eCRF.

7.3.1.6 Infusion-Related Reactions to Pembrolizumab

Pembrolizumab may cause severe or life-threatening IRRs including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. For full details regarding the warning and precautions related to pembrolizumab treatment, refer to the current version of the local product label. For guidance on dose modification and toxicity management of pembrolizumab-associated IRRs, refer to the local prescribing information or institutional guidance.

7.3.2 Docetaxel

7.3.2.1 Risk Associated with Docetaxel

For full details regarding warning and precautions relating to docetaxel treatment, refer to the current version of the local product label.

Table 7-4 Side Effects Associated with Docetaxel

Most Common Side Effects	Less Common Side Effects (may be severe or life-threatening)
• Myelosuppression with/without infection or bleeding (may be severe) • Hypersensitivity reaction (may be severe) • Fluid retention (may be severe) • Neuropathy (may be severe) • Cutaneous effects including nails (may be severe) • Alopecia • Gastrointestinal events such as nausea, vomiting, stomatitis, and diarrhea • Fatigue • Musculoskeletal pain • Lacrimation/tear duct obstruction	• Secondary malignancy/leukemia • Cardiotoxicity, arrhythmia • Pneumonitis • Gastrointestinal obstruction, perforation, and/or hemorrhage • Arterial or venous thromboembolism • Disseminated intravascular coagulation • Seizures • Hepatotoxicity

Due to the ethanol content in the docetaxel formulation, some subjects may experience intoxication during and after treatment. Refer also to the warnings and precautions of the local prescribing information for docetaxel.

7.3.2.2 Management of Specific Adverse Events with Docetaxel

Follow the dose recommendations in the local prescribing information for docetaxel as well as the suggested docetaxel dose reductions below.

Table 7-5 Docetaxel Dose Reduction

Dose Level	Docetaxel
Maximum dose	75 mg/m^2
First reduction	55 mg/m^2
Second reduction	37.5 mg/m^2

For EC9 (GEN1046 – docetaxel combination), administration of prophylactic G-CSF or pegylated G-CSF is recommended with every cycle in order to prevent febrile neutropenia and prolonged severe neutropenia.

All implemented dose modifications are permanent and dose escalation is not permitted. Refer to approved label for complete product information about docetaxel.

7.3.2.3 Other Specific Docetaxel Toxicities Not Requiring Dose Adjustment

Subjects should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm or, very rarely, fatal anaphylaxis have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy. Subjects with a history of severe hypersensitivity reactions should not be rechallenged with docetaxel.

Hypersensitivity reactions may occur within a few minutes following initiation of docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of the therapy is not required.

7.3.3 Cisplatin and Carboplatin

Cisplatin for injection can cause dose-related nephrotoxicity and peripheral neuropathy as well as myelosuppression and ototoxicity. Without antiemetic medication, marked nausea and vomiting occur in almost all patients. Consider alternative treatments or reduce the dose of cisplatin for injection for patients with baseline renal impairment or who develop significant reductions in CrCl during treatment with cisplatin for injection according to clinical treatment guidelines (Note: Refer to inclusion criterion 7.1.d for the trial-specific inclusion criterion for renal function).

Carboplatin also causes myelosuppression. Peripheral neurologic toxicity is generally common and mild. As with other platinum-based compounds, hypersensitivity reactions may occur. Patients with pre-existing severe renal impairment should not receive treatment with carboplatin (Note: Refer to inclusion criterion 7.1.d for the trial-specific inclusion criterion for renal function).

Investigators may switch subjects from cisplatin to carboplatin during the course of the trial if toxicities occur. If the cisplatin dose was modified prior to switching, the subject may start at a carboplatin dose level 0 and will be eligible to receive an additional 2 dose modifications of carboplatin. The dose of cisplatin or carboplatin may be reduced or held according to the guidelines provided in Table 7-6. Dose modification according to Table 7-6 is allowable at the investigator's discretion for intolerable Grade 2 to 3 toxicities not specified in Table 7-7 and Table 7-8. Investigators may also follow the local label or institutional standard for dose modifications and management of chemotherapy-related AEs. The dose modification decisions must be documented in the subject's trial records and reported in the case report form (CRF).

Table 7-6 Dose Modification for Cisplatin and Carboplatin

Drug	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin	100 mg/m^2	80 mg/m^2 (20% decrease)	64 mg/m^2 (20% decrease)	Discontinue
Cisplatin[1]	75 mg/m^2	56 mg/m^2 (20% decrease)	38 mg/m^2 (20% decrease)	Discontinue
Carboplatin[1]	AUC 5	AUC 4 (20% decrease)	AUC 3 (20% decrease)	Discontinue
Carboplatin[2]	AUC 6	AUC 5 (20% decrease)	AUC 4 (20% decrease)	Discontinue

AUC=area under the curve.
1 For subjects with non-squamous NSCLC, CPI-naïve regardless of PD-L1 status.
2 For subjects with squamous NSCLC, CPI-naïve regardless of PD-L1 status.

Table 7-7 Cisplatin or Carboplatin Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

Adverse Event	Number of Occurrences	Treatment Modification
Febrile neutropenia[1]	1	Reduce by 1 dose level. The use of growth factors and antibiotics should be considered per local standards.
Documented infection	2	Reduce by 1 dose level. Consider prophylactic antibiotics for subsequent cycles. The use of growth factors should be strongly considered per local standards.
	3	Discontinue platinum treatment (cisplatin or carboplatin).

1 Absolute neutrophil count <1000/mm^3 (1.0 x 10^9/L) and a single temperature >38.3°C or sustained temperature ≥38°C for >1 hour.

Table 7-8 Dose Modification Guidelines for Cisplatin or Carboplatin Drug-Related Adverse Events

Category	Toxicity	Hold Platinum Treatment for Grade	Timing for Restarting Platinum Treatment	Dose for Restarting Platinum Treatment	Discontinue Platinum Treatment
Hematologic	Neutropenia	3[1]	Neutrophil count resolves to ≥1,000/mm^3 (1.0 x 10^9/L)	No reduction *consider G-CSF	Toxicity does not resolvewithin 12 weeks of last infusion or if >2 DL reductions exceeded
		4[1]	Neutrophil count resolves to ≥1,000/mm^3 (1.0 x 10^9/L)	Reduce by 1 DL *consider G-CSF	Toxicity does not resolvewithin 12 weeks of last infusion or if >2 DL reductions exceeded
	Thrombocytopenia	2	Platelet count resolves to ≥75,000/mm^3 (75 x 10^9/L) or baseline	No reduction	Toxicity does not resolve within 12 weeks of lastinfusion or if >2 DL reductions exceeded
		3-4[1]	Platelet count resolves to ≥75,000/mm^3 (75 x 10^9/L) or baseline	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of lastinfusion or if >2 DL reductions exceeded
Non-hematologic	Creatinine increased	2-4[1]	Toxicity resolves to grade 0-1	For subjects taking carboplatin, reduce by 1 DL. For subjects taking cisplatin, change cisplatin to carboplatin.	Toxicity does not resolvewithin 12 weeks of last infusion or if >2 DL reductions exceeded
	Ototoxicity or sensory neuropathy	2	Change cisplatin to carboplatin May continue treatment with carboplatin		
		3-4	May switch cisplatin to carboplatin if resolved to grade ≤2 within 12 weeks of last infusion If already using carboplatin, then discontinue		
	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of lastinfusion or if >2 DL reductions exceeded
	Laboratory AE[2]	4	Toxicity resolves to grade 2 or less	Reduce by 1 DL	Toxicity does not resolve within 12 weeks

Category	Toxicity	Hold Platinum Treatment for Grade	Timing for Restarting Platinum Treatment	Dose for Restarting Platinum Treatment	Discontinue Platinum Treatment
					of lastinfusion or if >2 DL reductions exceeded

AE=adverse event; DL=dose level; G-CSF=granulocyte colony stimulating factor.
1 Permanent discontinuation should be considered for any severe or life-threatening event. Consult sponsor before restarting treatment after grade 4 drug-related AE.
2 Subjects with intolerable or persistent grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from trial drug for persistent grade 2 adverse reactions for which treatment has been held and did not recover to grade 0 to 1 within 12 weeks of the last infusion. With investigator and sponsor agreement, subjects with a laboratory AE still at grade 2 after 12 weeks may continue in the trial only if asymptomatic and controlled.

7.3.4 Paclitaxel

Paclitaxel causes dose-dependent myelosuppression (primarily neutropenia), as well as peripheral sensory or motor neuropathy. Gastrointestinal symptoms and alopecia are commonly associated with paclitaxel. Local infusion reactions are very common and moderate and severe hypersensitivity reactions may occur. Patients with a baseline neutrophil count $<1.5 \times 10^9$/L or patients with severe renal impairment (GFR <30 mL/min) should not be treated with paclitaxel.

For dose modification related to paclitaxel toxicities refer to Table 7-9. Investigators should follow the local label or SOC for dose modifications and management of chemotherapy-related AEs.

The dose of paclitaxel may be reduced at the discretion of the clinician according to the guidelines provided below in Table 7-10.

Table 7-9 Dose Modification Guidelines for Paclitaxel

Event	Suggested Dose Modification for Toxicity
Myelotoxicity	Treatment with paclitaxel should be delayed until the absolute neutrophil count is >1500/µL and platelet count is >100,000/µL. If a subject developed severe neutropenia (<500/µL) for a week or longer, or febrile neutropenia during the prior course, then the paclitaxel dose should be reduced by 20% to 25% for subsequent courses. An alternative to dose reduction is the institution of hematopoietic growth factor support.
Hepatic toxicity	Paclitaxel dose may need to be adjusted for hepatic impairment on Day 1 of each cycle.
Neurotoxicity	For grade 2 or worse sensory or motor peripheral neuropathy, interrupt therapy until resolved to grade 1 or less and reduce dose by 20% for subsequent therapy. For delay in recovery >2 weeks or worsening neuropathy consider discontinuing. For subjects who develop severe neuropathy (grade 3 or 4) for a week or longer, the dose of paclitaxel should be reduced by 20% for subsequent courses.
Diarrhea	For grade 3 or worse diarrhea on day of treatment, hold paclitaxel. Once resolved to grade 1 or less, reduce dose by 20%.
Mucositis	For grade 3 or worse mucositis, hold paclitaxel until resolved to grade 1 or less, reduce dose by 20%. For second occurrence or if grade 3 >2 weeks consider discontinuing.
Other nonhematologic events	For all other nonhematologic grade 3 or worse events (except alopecia, constipation, nausea, and infusion reactions), hold therapy until resolved to grade 1 or less.

Table 7-10 Dose Modification for Paclitaxel

	Full dose	First dose reduction	Second dose reduction	If additional dose reduction required
Paclitaxel	200 mg/m^2	150 mg/m^2	112.5 mg/m^2	Discontinue

7.3.5 Nab-paclitaxel

Nab-paclitaxel has overall a similar safety profile to paclitaxel. There are, however, rare occurrences of severe hypersensitivity reactions. Subjects who have baseline neutrophil counts <1500 cells/mm^3 should not be treated with nab-paclitaxel.

The dose of nab-paclitaxel may be reduced according to the guidelines provided below in Table 7-11. Trial treatment should be discontinued if a subject experiences toxicity that requires more than 2 dose reductions. Investigators should follow the local label or SOC for dose modifications and management of chemotherapy-related AEs.

Table 7-11 Dose Modification for Nab-paclitaxel

	Full dose	First dose reduction	Second dose reduction	If additional dose reduction required
Nab-paclitaxel	100 mg/m^2	75 mg/m^2	50 mg/m^2	Discontinue

7.3.6 Pemetrexed

Treatment with pemetrexed is associated with suppression of the bone marrow function, as manifested by neutropenia, thrombocytopenia, and anemia (or pancytopenia). Myelosuppression is usually the DLT. Subjects should not begin a new cycle of treatment unless the ANC is ≥1500 cells/mm^3, the platelet count is ≥100,000 cells/mm^3.

Pemetrexed is secreted renally and it should not be administered to subjects whose CrCl is <45 mL/min (Note: Refer to inclusion criterion 7.1.d for the trial-specific inclusion criterion for renal function).

Dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. For dose modification related to pemetrexed toxicities refer to Table 7-12 and Table 7-13.

Table 7-12 Pemetrexed Dose Modification Guidelines for Hematological Toxicity

Platelets μL	ANC 10^9/L	Dose Level
≥50,000 AND	≥ 0.5	No reduction
≥50,000 AND	< 0.5	Reduce by 1 DL
<50,000 without bleeding AND	ANY	Reduce by 1 DL
<50,000 with grade ≥ 2 bleeding AND	ANY	Reduce by 2 DL
ANY AND	< 1.0 + fever ≥ 38.5°C (101°F)	Reduce by 1 DL

ANC=absolute neutrophil count; DL=dose level.

Table 7-13 Pemetrexed Dose Modification Guidelines for Non-Hematological Toxicity

Event	CTCAE Grade	Dose level
Nausea or vomiting	Grade 3 or 4	No reduction
Diarrhea	Grade 3 or 4	Reduce by 1 DL
Mucositis	Grade 3 or 4	Reduce by 2 DL
Neurotoxicity	Grade 2	No reduction
	Grade 3 or 4	Reduce by 1 DL
Transaminase elevation	Grade 3	Reduce by 1 DL
	Grade 4	Discontinue
Other non-hematological toxicity	Grade 3 or 4	Reduce by 1 DL

CTCAE=Common Terminology Criteria for Adverse Events; DL=dose level.

The dose of pemetrexed may be reduced according to the guidelines provided below in Table 7-14. Trial treatment should be discontinued if a subject experiences toxicity that requires more than 2 dose reductions. Investigators should follow the local label or SOC for dose modifications and management of chemotherapy-related AEs.

Table 7-14 Dose Modification for Pemetrexed

	Full dose	First dose reduction	Second dose reduction	If additional dose reduction required
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue

7.3.7 Pembrolizumab

Please refer to the local label of pembrolizumab.

7.3.7.1 Risks Associated with Pembrolizumab

Table 7-15 Side Effects Associated with Pembrolizumab

Most Common Side Effects (≥20% of patients)	Less Common Side Effects (may be severe or life-threatening)
• Fatigue • Cough • Nausea • Pruritus • Rash • Decreased appetite • Constipation • Arthralgia • Diarrhea	• Immune-related AEs • Infusion-related reactions, see Section 7.3.1.6 • Please refer to the local label of pembrolizumab and Table 7-1

AE=adverse event.

7.3.7.2 Management of Specific Adverse Events with Pembrolizumab

Dose reductions are not recommended for pembrolizumab. Dose should be withheld or treatment permanently discontinued for specified events; please refer to Section 7.3 and Table 7-1 and the local prescribing information for pembrolizumab.

7.4 Safety Stopping Rules

Treatment with trial treatment should be discontinued due to safety concerns under the following conditions:

- If the subject experiences a TRAE that meets the criteria for treatment discontinuation as specified in Table 7-1, Table 7-2, or Table 7-3.
- An AE that fails to resolve to ≤ grade 1 within 21 days due to a toxicity possibly related to GEN1046, unless otherwise approved by the sponsor medical monitor.
- Treatment-related grade 4 or life-threatening AE, except with approval from the medical monitor.
- Second occurrence of an IRR of ≥ grade 3 despite premedication prior to the second infusion.
- First occurrence of anaphylaxis or a grade 4 IRR.

Please note:

- Regardless of the reason for discontinuation, the subject should be examined as soon as possible (refer to Section 8.1 for details regarding discontinuation of treatment).

8 DISCONTINUATION, FOLLOW-UP, AND COMPLETION

8.1 Discontinuation of Treatment

Subjects will receive GEN1046 treatment on Day 1 of each 3-week or 6-week treatment cycle until one of the predefined discontinuation of treatment criteria (below) has been met.

- Radiographic disease progression or confirmed radiographic disease progression by iRECIST (if applicable refer to Section 9.2)
- Clinical progression
- Lost to follow-up
- Subject requests to discontinue treatment
- Death
- Unacceptable AEs requiring trial treatment discontinuation (refer to Safety Stopping Rules – Section 7.4)
- Investigator believes that it is in the best interest of the subject to stop trial treatment
- Withdrawal of consent
- Pregnancy

CCI [redacted]

Refer to the Schedule of Activities in Section 1.3.2 for details on unscheduled visits for safety laboratory assessments for subjects who have discontinued GEN1046 and entered safety follow-up. For subjects who derive benefit from GEN1046 monotherapy (EC8) or added benefit from GEN1046 in combination with pembrolizumab +/-chemotherapy (EC11A, EC11B, EC12, and EC13), the investigator in discussion with the subject may consider having the subject remain in the trial to receive all trial treatments including GEN1046, and in consultation with the Genmab Medical Director.

Subjects in the docetaxel combination cohort EC9 will receive docetaxel treatment in combination with GEN1046 on Day 1 of each 3-week treatment cycle until PD, or until 1 of the predefined discontinuation of treatment criteria has been met. Subjects may only continue on GEN1046 or docetaxel monotherapy if approved by sponsor's medical monitor. Subjects move into the safety follow-up period once both drugs have been discontinued.

Subjects in the pembrolizumab combination cohorts EC11A and EC11B will receive pembrolizumab treatment in combination with GEN1046 on Day 1 of each 3-week treatment cycle or on Day 1 of each 6-week treatment cycle, respectively, until PD, or until 1 of the predefined discontinuation of treatment criteria has been met. Subjects may only continue on

GEN1046 or pembrolizumab monotherapy if approved by sponsor's medical monitor. Subjects move into the safety follow-up period once both drugs have been discontinued.

For subjects on combination therapy consisting of GEN1046, pembrolizumab, and platinum-based chemotherapy doublets in cohorts EC12 and EC13, respectively, if 1 or both chemotherapeutic agents is discontinued due to treatment-related AE, the subject may continue with the remaining components of the treatment regimen; if GEN1046 and/or pembrolizumab are/is discontinued due to treatment-related AE, the subject may continue with the remaining components of the treatment regimen, and will be considered on treatment.

If GEN1046 treatment is permanently discontinued for other reasons than radiographic disease progression, every effort should be made to continue tumor assessments according to the schedule of activities.

Subjects should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible and the treatment discontinuation visit should be performed. If the treatment discontinuation visit coincides with a regularly scheduled cycle visit, the treatment discontinuation evaluations will supersede those of the regularly scheduled cycle visit.

8.2 Withdrawal from the Trial

Subjects will be withdrawn from the trial (dose escalation or expansion) for the following reasons:

- Subject withdraws consent from the trial including survival status follow up
- Sponsor decision
- Lost to follow-up (see Section 8.5)
- Subject died
- Trial closure
- Other

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. A subject may choose to discontinue from any future trial assessments (eg, dosing, imaging, blood sampling, etc) but agree to remain in the trial and to be followed for survival follow-up, without withdrawal of consent.

If a subject withdraws from the trial, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

The sponsor will make any effort to ensure subjects are followed up for completion of safety assessment in the trial. See the Schedule of Activities (Section 1.3) for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.

Trial treatment assigned to the withdrawn subject may not be assigned to another subject.

8.3 Withdrawal from the Use of Research Samples

The subject may withdraw their consent for future use of research samples at any time. To initiate the sample destruction process, the investigator must notify the sponsor of withdrawal of consent for the research samples and to request sample destruction. The sponsor will then initiate the process for sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed. If the subject withdraws consent for research samples, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Samples will be destroyed after they are no longer needed for the clinical trial. Details of the sample retention for research are presented in the ICF and in Section 13.2.7.

8.4 Safety Follow-Up Evaluations

Subjects discontinuing from treatment for any reason will have safety follow-up visits 30 days (±5 days) and 60 days (±7 days) after the subject receives the last dose of trial treatment. If the subject initiates new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anti-cancer treatment. After the safety follow-up visits, the subject will move into survival follow-up.

8.5 Lost to Follow-Up

For subjects whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw consent, the investigator should show “due diligence” by contacting the subject, family, or family physician as agreed in the ICF and by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc. A subject should not be considered lost to follow-up until due diligence has been completed (as a minimum 3 documented attempts).

9 ASSESSMENTS

9.1 Demography and Baseline Characteristics

9.1.1 Demographics

Year of birth and/or age, race, ethnic origin, gender, and smoking and drinking habits will be assessed at screening.

9.1.2 Disease Status

Primary site of cancer and initial and current disease stage (Tumor Nodes Metastasis staging system) will be recorded at screening.

For subjects with:

- All tumor types in the expansion or escalation: PD-L1 status as per local assessment (if available)
- NSCLC: the subjects' tumor status with respect to EGFR mutations and ALK/ROS1 rearrangement as per local assessment
- Endometrial cancer and TNBC: dMMR or MSI status as per local assessment (if available)
- TNBC: HER2 status, ER, and PgR negative status as per local assessment
- SCCHN: HPV status as per local assessment (if available)
- Cervical Cancer: HPV status as per local assessment (if available)

9.1.3 Medical History

Any medical condition (signs, symptoms, and diagnosis) occurring prior to first dose of trial treatment should be documented in the source documents as medical history. Medical conditions that occur after the ICF is signed and prior to first GEN1046 dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.

Any medical history/current medical condition that worsens after the first dose of trial treatment will be documented as an AE.

9.1.4 Concomitant Medication

Any medication or therapy (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, and blood transfusions) other than GEN1046 is considered concomitant medication and should be recorded with the following information:

- Start date
- Route of administration and frequency

- Stop date of administration or ongoing at trial termination
- Indication/reason for use
- The total daily dose should be filled in whenever possible

Relevant prior concomitant medication administered during the trial must be recorded from 21 days prior to the first dose of GEN1046 and up to 60 days after the last dose of trial treatment.

The subject must be told to notify the investigational site about any new medications he or she takes after the start of GEN1046.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

9.1.5 Prior Cancer Therapy and Surgery

Administration of prior anti-cancer therapies**,** including surgery, radiotherapy, chemo-radiotherapy, systemic treatment regimens, etc, from the time of initial diagnosis until enrollment in this trial will be documented. In addition**,** the best response, reason for discontinuation, dates of administration, and progression should be reported for anti-cancer therapies.

9.2 Efficacy Assessment

All subjects will have imaging of the brain, thorax, abdomen, and pelvis performed during screening. Head and neck imaging is always required for subjects with SCCHN. Imaging of the pelvis is not required for subjects with SCCHN but is strongly recommended.

Tumor imaging is strongly preferred to be acquired by CT. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. Localized CT with contrast or MRI (with or without contrast; for sarcomas with contrast) must be acquired for assessment of lesions of the skeleton/extremities and head and neck if not visible on other images. At the discretion of the investigators and after approval of the sponsor, combined PET/CT (eg, FDG-PET) may be performed for tumor assessments as per RECIST 1.1, but only if the CT portion is of similar diagnostic quality to CT alone.

The same imaging modality and ideally the same scanner should be used throughout the trial to optimize the reproducibility of the assessment and preserve the accuracy of the assessment of response or progression. Chest x-rays and ultrasound should not be used to measure tumor lesions.

9.2.1 Definition of Target and Non-target Disease

Up to 5 target lesions as per RECIST 1.1 (maximum 2 per organ; >10 mm in diameter, long axis; >15 mm for nodal lesions, short axis) will be selected at screening and must be followed throughout the trial. Previous irradiated lesions(s) with documented progression may be considered target lesion(s), after discussion with and approval by the sponsor medical director. Non-target lesions will also be assessed throughout the trial. Lesions located in an area subjected to other loco-regional therapy should be followed as non-target lesions.

Each lesion must be evaluated using the same imaging modality/methodology throughout the trial and when possible, by the same local radiologist/physician to ensure consistency. Imaging of lesions at screening must be taken within 21 days before C1D1. Images taken within 21 days before C1D1, as part of routine clinical management, are acceptable if they are of diagnostic quality. Furthermore, images exceeding the 21-day window may be used for enrollment, after approval by the sponsor medical director.

As a rule, target lesions must not be biopsied in this trial. Under exceptional circumstances, a biopsy may be taken on a target lesion, after discussion with and approval by the sponsor medical director. Such exceptions are particularly relevant for single target lesions. If a biopsy at screening is allowed, the lesion must be imaged before being biopsied.

On-trial imaging will be performed 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 (unless the investigator elects to continue treatment and follow iRECIST), 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.

In dose escalation and expansion, the reading of the scans will be done by a local radiologist. Sites should attempt to maintain the same radiologist throughout the trial. Results from the radiology evaluations shall be recorded in the eCRF and a copy of the evaluation reports should be kept in the subject's file. RECIST 1.1 criteria will be used for secondary endpoint response evaluation (Eisenhauer et al., 2009); iRECIST will be used for exploratory endpoint response evaluation (Seymour et al., 2017). If the investigator elects to apply iRECIST, treatment should continue until PD has been verified.

Additional CT scans or MRI scans may be performed at the investigators discretion to confirm response or new symptoms. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. In this case, the investigator must choose the imaging technology based on the clinical indication. Images obtained at an unscheduled time point that determine disease progression should be captured in the eCRF for subjects enrolled in the expansion part.

9.2.2 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but has been modified to account for the unique response patterns observed with immunotherapy. In this trial, iRECIST will be evaluated as an exploratory endpoint (Seymour et al., 2017).

iRECIST disease progression should be confirmed at least 4 to 7 weeks after the first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on trial treatment until progression is confirmed as long as the subject is clinically stable. Subjects who are clinically stable must meet the following criteria:

- Subject must have clinical benefit from continuation of trial treatment (as assessed by the investigator) and must not have rapid disease progression
- Subject is tolerating trial treatment
- Subject must have a stable ECOG status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications for disease progression (eg, CNS metastases requiring immediate treatment).

Any clinically unstable subjects should be discontinued from trial treatment at the first occurrence of radiographic disease progression. Subjects that are clinically unstable are not required to have repeated imaging to confirm PD by iRECIST however, a confirmation of progression scan may be obtained at the investigator's discretion after consultation with the sponsor.

If repeat imaging shows iRECIST confirmed disease progression (iCPD), subjects will discontinue trial treatment. However, if the subject is deriving benefit after iCPD is observed, an exception to continue trial treatment must be approved by the sponsor medical monitor. If repeat imaging shows iRECIST stable disease (iSD), iRECIST partial response (iPR), or iRECIST complete response (iCR), imaging should be continued every 6 weeks (±7 days) and the subject should continue on trial treatment. Subjects who have repeat imaging to confirm progression do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later.

9.2.3 Survival Status

Survival status will be assessed every 12 weeks (±14 days), beginning from the day of last dose of trial treatment and continuing until the subject dies or withdraws from the trial. Subjects may be contacted by telephone, email, or visit. Survival status may be requested more frequently around the time of a database lock. Subjects who are not or whose designated family members are not available for this assessment should be entered as "lost to follow-up" (Section 8.5).

9.3 Pharmacokinetics

9.3.1 Evaluations

Venous blood samples will be collected for measurement of plasma concentrations of GEN1046 as specified in Table 1-3 (Dose Escalation), and Table 1-12, Table 1-13, Table 1-14, Table 1-15, and Table 1-16 (Expansion).

The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of GEN1046. Venous blood samples will be collected and each plasma sample will be divided into aliquots. Samples collected for analyses of plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained.

9.3.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of GEN1046 using validated methods.

9.4 Clinical Safety Assessments

9.4.1 Physical Examination

The investigator or qualified designee will perform a full physical examination according to SOC during the screening period. Report any relevant findings as medical history. Report any medical conditions as an AE if they were assessed by the investigator to have been caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of

prior medications. After the first dose of GEN1046, report any new or worsening findings since the last assessment as AEs. The time points for full physical examinations are described in the Schedule of Activities (Section 1.3).

9.4.2 Vital Signs

Vital signs, including temperature, blood pressure, and heart rate, should be measured with the subject in a supine or reclined position and recorded. Within each visit, preferably the same equipment shall be used for vital sign measurements. On infusion days, vital signs should be assessed as indicated in the Schedule of Activities (Section 1.3). On non-infusion days, vital signs should be assessed any time during the visit.

9.4.3 Electrocardiograms

The ECGs will be recorded digitally at the sites by using the standard 12-leads as outlined in Section 1.3. ECGs will be performed in accordance with the ECG manual issued by the vendor. 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 cardiologist. After the primary analysis cutoff date, ECGs will be performed locally if clinically indicated at an unscheduled visit and will no longer be submitted to a central laboratory.

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable. The investigator ECG interpretation must be done using the paper ECG reading from the ECG machine by signing and dating the printout. In case of discrepancy between central and the investigator ECG readings, the central reading will be used for trial analysis purposes.

For the ECG recordings, the subjects must be resting and in a supine or reclined position for at least 10 minutes. Any irregularity observed or occurring during the ECGs (eg, vomiting, cough) should either induce a repeat of the ECG or be annotated on the eCRF with the description and time of the occurrence.

9.4.4 ECOG Performance Status

The ECOG performance status will be assessed by the investigator at screening, on Day 1 of each cycle, and at the treatment discontinuation visit. Performance status will be scored using the ECOG performance status scale index.

Table 9-1 ECOG Performance Status

Score	Definition
0	Fully active, able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead.

ECOG=Eastern Cooperative Oncology Group.

9.5 Clinical Laboratory Assessments

Central and Local Laboratory

Central and local laboratories will be used for analysis of the tests detailed in Table 9-2 according to the visit schedule outlined in the Schedule of Activities (Section 1.3). After the primary analysis cutoff date (Section 11.12.2), only local laboratory tests will be collected.

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

The investigator must review the central laboratory results, document this review, and record any clinically relevant changes occurring during the trial in the AE section of the eCRF.

Table 9-2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology (centrally and locally)	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC %Reticulocytes		WBC Count with Differential*: Neutrophils Lymphocytes Monocytes Eosinophils Basophils *local labs will collect differential as per local standard of care. Central labs will collect differential as both % and absolute.
Biochemistry (centrally and locally)	Albumin	BUN (Blood urea nitrogen)	Gamma-glutamyl transferase	Phosphate
	Alanine aminotransferase (ALT)	Calcium	Glucose	Potassium Sodium
	Alkaline phosphatase	Chloride	Glycosylated hemoglobin	Total and direct bilirubin
	Amylase	C-reactive Protein	Lactate dehydrogenase	Total protein
	Aspartate aminotransferase (AST)	Creatinine (GFR calculation)	Lipase Magnesium	Uric acid Ferritin[1]
Coagulation factors (only locally)	Prothrombin time	International normalized ratio (INR)	Activated partial thromboplastin time (aPTT)	
Urinalysis (only locally)	Leukocytes	Protein	Urine pregnancy	
Endocrine (only centrally)	TSH	Free thyroxine (T4)	Total triiodothyronine (T3)[2]	
Other screening tests (only centrally)	Serum beta-hCG[3] Hepatitis B			

NOTE: After the primary analysis cutoff date (Section 11.12.2), only local laboratories will be used.
beta-hCG=beta-human chorionic gonadotropin; GFR=glomerular filtration rate; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; TSH=thyroid stimulating hormone; WBC=white blood cell.

[1] Refer to Section 7.3.1.3.2 for additional analytes to monitor if HLH is suspected.
[2] Free T3 is acceptable if considered local standard.
[3] Serum beta-hCG should be collected at screening only.

Eligibility Assessment Based on Laboratory Values

Central laboratory values for hematology, biochemistry, endocrine, serum (beta-hCG) pregnancy, and hepatitis B will be used for assessment of eligibility. Coagulation factors and urinalysis must be performed locally to assess for eligibility. Central and local laboratory samples at the screening visit must be obtained within 7 days prior to C1D1 with the exception of hepatitis B (which may be obtained earlier). However, if the central laboratory values obtained during screening are unexpectedly unavailable when the subject is scheduled for the first administration of GEN1046, local laboratory values may be used following agreement with the sponsor's medical monitor.

Treatment Decisions Based on Laboratory Values

Local and central laboratory samples should be obtained on Day 1 of each cycle or up to 3 days before for Cycle 2 and beyond. Every effort should be made to obtain local and central labs on the same day. Hematology, biochemistry, and endocrine labs should be obtained centrally. Hematology, biochemistry, coagulation factors, urine pregnancy, and urinalysis should be performed locally. Local labs should be used for treatment decisions and take precedence over central laboratory values.

Central laboratory samples will not be collected after the primary analysis cutoff date (Section 11.12.2).

Laboratory Assessments at Treatment Discontinuation, 30-Day Safety Follow-Up, and 60-Day Safety Follow-Up Visits

Hematology, biochemistry, and hepatitis B samples obtained during the listed visits in the Schedule of Activities (Section 1.3) are analyzed at the central laboratory only, while coagulation factors analysis and urinalysis (including pregnancy test, if applicable) are performed only locally.

Central laboratory samples will not be collected after the primary analysis cutoff date (Section 11.12.2).

9.6 Immunogenicity

9.6.1 Evaluations

Venous blood samples will be collected for measurement of serum concentrations of ADAs as specified in the Schedule of Activities (Section 1.3).

Samples will be used to evaluate the presence of ADAs to GEN1046. Samples collected for ADAs to GEN1046 may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period for further characterization of immunogenicity.

Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9.6.2 Analytical Procedures

The detection and characterization of antibodies to GEN1046 will be performed using validated methods under the supervision of the sponsor.

9.6.3 Immunogenicity Assessments

ADAs to GEN1046 will be evaluated in serum samples collected from all subjects according to the visit schedule. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to GEN1046 and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of ADAs to GEN1046 and/or further characterize the immunogenicity of GEN1046.

9.7 Biomarkers

Biomarker investigations in this trial will include pharmacodynamic biomarkers to confirm biological activity of GEN1046, and predictive biomarkers that may identify subjects that can benefit from GEN1046 as monotherapy or in combination. Where required by local or country-specific regulations, each subject must sign a separate ICF if he or she agrees to provide samples for genomic biomarker analysis (DNA and RNA). If a subject refuses to consent to DNA and RNA research in these specific regions, the subject is still eligible to participate in the trial.

Biomarker assessments will focus on:

- CCI
- CCI
- CCI
- CCI

All retrospective biomarker assessments will be performed at a central laboratory and specialty labs.

9.7.1 Biomarker Assessments in Tumor Samples

In dose escalation, all subjects must provide a tumor tissue sample (FFPE blocks/slides) from archival tissue or fresh tumor biopsy collected before C1D1, preferably derived from advanced stage disease.

In the expansion part, for EC1 to EC7, EC9, and EC10, all subjects must provide a mandatory fresh FFPE core-needle biopsy which contains tumor tissue and is taken after failure/stop of last prior treatment and prior to the first GEN1046 infusion. Documentation of the fresh FFPE biopsy collection must be submitted to the sponsor as a part of the eligibility package prior to

administration of first dose of GEN1046. Furthermore, the latest archival tumor tissue sample, which has been taken before failure/stop of last prior treatment, should be collected, if available.

For EC8, EC11, EC12, and EC13, all subjects must (EC8, EC12, and EC13)/should (EC11) provide an FFPE tumor sample obtained prior to C1D1 that is of sufficient histological quality and has preserved tissue architecture (ie, core-needle biopsies, histological punctures, biopsies performed with mini-forceps, resections) and must originate from the metastatic stage of the cancer. The tumor tissue should ideally be from the same block of tumor used for local PD-L1 testing, if applicable.

In the expansion cohorts with selection of subjects with PD-L1+ tumors only, the following applies:

- When prospective central PD-L1 testing is required (mandatory in EC10, optional in EC8 and EC11 in case local testing is not feasible/acceptable), the tumor sample should be submitted to the central laboratory as soon as possible after informed consent has been obtained in order to have the PD-L1 expression result available prior to C1D1. NOTE: C1D1 must be performed no later than 35 days after informed consent has been obtained.

All subjects in expansion must also have on-treatment fresh FFPE tumor biopsies (as described in Table 1-18, Table 1-19, Table 1-20, Table 1-21, and Table 1-22), which should be collected after the second dose of GEN1046, after the fourth dose of GEN1046 for EC8 and EC10 only, and at disease progression (preferably from a new lesion if any) or treatment discontinuation where it is considered feasible without a risk of complications for the subject. If deemed necessary by the investigator, the subject may be called in for an unscheduled visit during dose escalation and dose expansion; optional tumor biopsies may be collected if subjects have unscheduled biopsies or tumor tissue resection during the course of the trial.

All tumor samples for central biomarker evaluation and tumor samples used for local PD-L1 testing in EC8 and EC11 must be of sufficient histological quality and have preserved tissue architecture (ie, core-needle biopsies, histological punctures, biopsies performed with mini-forceps, resections are accepted). The following samples are not acceptable for this trial: fine needle aspirates, cell blocks, cell pellets, clots, bone marrow or decalcified bone tissue, and any cytological specimens (smears, brushings, washings, lavages, and effusions). Tissue samples should not have been previously irradiated. FFPE tissue blocks are preferred to slides. Details on FFPE tissue block submission or the preparation of slides/number of slides to be prepared will be described in the laboratory manual. In case it is not feasible to meet the required tumor tissue criteria in escalation or expansion, the sponsor medical monitor's approval for enrollment is needed.

In the expansion part, biomarker analyses in tumor samples at baseline, during treatment (after 2 full doses of GEN1046), and/or upon tumor progression may help confirm GEN1046's MoA and enable the identification of biomarkers predictive of response and resistance to GEN1046 as monotherapy or in combination. CCI [redacted]

RNA Expression Analyses

RNA sequencing may be performed on tumor biopsies to determine PD-L1 and 4-1BB expression levels, immune signatures based on gene expression, and expression of other genes related to GEN1046's MoA (eg, CCI , etc) or disease biology.

DNA Analyses

Tumor biopsies may also be analyzed using whole exome Next Generation Sequencing to determine TMB, MSI status, T-cell receptor (TCR) and B-cell receptor diversity and changes in clonality, mutations/insertions/deletions in genes associated with resistance to PD-L1/PD-1 therapies (such as CCI). Other analyses may be performed to further understand and characterize disease biology, GEN1046's MoA, and subject response to this therapy.

Protein Expression Analyses

PD-L1 and 4-1BB expression, CCI may be evaluated in tumor biopsies by IHC on an automated staining platform. Tumor sections will be scored by a certified pathologist, and digital images will be made from stained tumor sections in order to be used for pathology analyses.

9.7.2 Biomarker Assessments in Blood Samples

Biomarker assessments may also be performed using whole blood samples to investigate potential pharmacodynamic markers and explore the relationship to efficacy and/or MoA of GEN1046. Assessments will be performed at baseline (before infusion at C1D1) and at later cycles during treatment in order to enable correlation analyses with response to treatment or disease biology.

Immunophenotyping Analyses

Immunophenotyping may be performed (eg, measurement of T cells, B cells, NK cells, monocytes, DC's) at baseline and during treatment at planned visits so changes associated with the MoA of GEN1046, subject response to GEN1046, and disease biology can be evaluated.

DNA Expression Analyses

CCI

RNA Expression Analyses

RNA sequencing may be performed on peripheral cells to determine PD-L1 and 4-1BB expression levels, immune signatures based on gene expression, and expression of other genes related to GEN1046's MoA (eg, CCI , etc) or disease biology.

Cell-Free DNA/RNA (cfDNA/RNA) and Circulating Tumor-Derived DNA (ctDNA) Analyses

CCI [redacted]

Exploratory PBMC Analyses

CCI [redacted]

9.7.3 Sample Collections

Samples for biomarker analyses will be collected as specified in Table 1-18, Table 1-19, Table 1-20, Table 1-21, and Table 1-22.

9.7.4 Additional Analyses

In addition to the biomarker analyses listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about GEN1046 (ie, mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing trials and/or literature data. Biomarker samples may further be used for up to 5 years after the last subject last treatment, to help address emerging issues and to enable the development of safer, more effective, and, ultimately, individualized therapy. Such analyses would be specific to research related to the trial drug or diseases being investigated by the sponsor.

Moreover, biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

10 SAFETY MONITORING AND ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

10.1 Adverse Event Definitions

10.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a clinical trial subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

AEs (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

10.1.2 Definition of Serious Adverse Event

An SAE is defined as an AE that meets one of the following criteria:

- Is fatal or life-threatening[1]
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Medical and scientific judgment must be exercised in deciding whether an AE is "medically important"
- Requires inpatient hospitalization or prolongation of existing hospitalization[2]

[1] The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

[2] Hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of the studied indication
- Solely due to progression of the underlying cancer
- Elective or pre-planned treatment for a pre-existing condition during trial that has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the subject's general condition
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above

10.1.3 Definition of Adverse Events of Special Interest

Adverse events of special interest (AESIs) are defined as events (serious or non-serious) which are of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

AESIs are defined on the basis of an ongoing review of the safety data. AESIs are discussed further in Section 10.4 and in the IB.

10.1.4 Definition of Infusion-Related Reactions

Infusion-related AEs are defined as any AEs occurring during infusion or where the onset of the event occurs within 24 hours after the end of infusion.

Investigators should consider the clinical picture and isolated events, such as "Fatigue", occurring within 24 hours after the end of infusion and assess whether or not it constitutes an IRR.

For IRRs the causality of the event (Section 7.3.1) should be judged as "related" by the investigator.

10.2 Reporting Period

This is trial-specific and defined in Section 10.2.1, Adverse Event Reporting. Events requiring immediate reporting are listed in Section 10.5.

10.2.1 Adverse Event Reporting

All AEs**,** whether serious or non-serious (see definitions in Section 10.1), will be documented from the first dose of trial treatment until 60 days after the last dose of trial treatment, subject withdrew consent, subject started new anti-cancer treatment, or the subject died, whichever comes first.

As noted in Section 9.1.3, any medical condition (signs, symptoms and diagnosis) occurring prior to first GEN1046 dose should be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE**.** Medical conditions (signs, symptoms, and diagnosis) that occur after the ICF is signed and prior to first GEN1046 dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications. For details regarding follow-up of AEs and SAEs, see Section 10.6.

10.2.2 Procedures for Recording and Reporting

All AEs, serious or non-serious, must be documented.

- The diagnosis/cause of an AE should be documented rather than the symptoms of the AE.
- If no diagnosis is available, then each sign and symptom should be documented as individual AEs.

- All AEs that occur during the AE reporting period must be documented, whether or not the event is considered treatment related.

- All AEs should be documented and reassessment made at each visit (or more frequently, if necessary).

- Final assessment of AEs must be performed by a medically qualified person.

Abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in trial treatment should be documented as an AE.

- Whenever possible, a diagnosis should be provided (eg, anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found.

NOTE: A CTCAE grade 3 or 4 laboratory abnormality does not automatically indicate an SAE.

Disease-related events and outcomes not qualifying as AEs or SAEs are trial-specific and provided in Section 10.3.1.

10.3 Evaluation of Adverse Events

Severity

Toxicities will be graded for severity according to CTCAE v5.0 to describe the intensity of AEs, with the exception of CRS, which will be graded according to the ASTCT criteria described by (Lee et al., 2019).

Relationship to the Investigational Medicinal Product

The investigator must assess whether or not the event is related to the trial drug. The relationship is to be judged using the following terms:

- Related

- Not related

If the relationship changes over time, the last judgment by the investigator should be reported. Relatedness has to be assessed and reported from the first time the event is being reported.

A suspected adverse reaction is one in which there is a reasonable possibility that the trial drug caused the AE, this means there is evidence to suggest a causal relationship between the trial drug and the AE (ie, considered related).

10.3.1 Disease-Related Events/Outcomes and Other Events/Procedures Not Qualifying as Adverse Events or Serious Adverse Events

10.3.1.1 Disease Progression or Death

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs or SAEs.

- That is, the terms “Disease Progression”, “Progression of Disease” or “Malignant Disease Progression” and other similar terms should not be used to describe an AE or SAE. These data are captured as efficacy assessment data only.
  - In most cases, the expected pattern of progression will be based on the response criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria.
  - Clinical symptoms that cannot be determined as reasonably due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study should be reported as an AE or SAE.
- Hospitalization due solely to progression of the underlying cancer should not be reported as an SAE. See Section 10.1.2, under the definition of SAE, for additional reasons when hospitalizations should not be reported as SAEs.

10.3.1.2 Unrelated Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, a medical condition for which an unscheduled procedure was performed should be reported if it meets the definition of an AE (an acute appendicitis should be reported as the AE and not the appendectomy).

10.4 Adverse Events of Special Interest

AESIs have not yet been defined for treatment with GEN1046.

10.5 Events Requiring Immediate Reporting

All SAEs, events of overdose, and/or medication errors must be reported to the sponsor within 24 hours of awareness. Safety Reporting Forms should be sent to the CRO within 24 hours via the electronic data capture (EDC) system. Only when the EDC system is down, or for Pregnancy reporting should the paper SAE reporting form or Pregnancy reporting form be used and forwarded to CCI .

10.5.1 Serious Adverse Events

SAEs must be reported from the investigational site to the sponsor no later than 24 hours following:

- The subject visit at which such AE was reported, noted or recognized;
- The principal investigator’s or any investigator personnel’s receipt of the test results or
- Other information from which such development was reported, noted, or recognized.

10.5.2 Overdose/Medication Errors

An overdose is defined as a subject receiving a dose of GEN1046 in excess of 10% of that specified in this protocol. All cases of overdose must be reported to the sponsor as protocol deviations within 24 hours of knowledge of the event (see additional details in Section 10.5.2.1).

Medication errors (including infusion rate errors) and uses outside what is foreseen in the protocol, including misuse and abuse of GEN1046, should be reported within 24 hours of knowledge of the event.

10.5.2.1 Treatment of Overdose

Rescue medication to reverse the action of GEN1046 is not available. In case of overdose, medication errors, misuse, and/or abuse of the trial drug, subjects should receive supportive care according to local guidelines and potential side effects of GEN1046 should be treated symptomatically.

In the event of an overdose, the investigator should:

- Contact the sponsor's medical monitor immediately.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis if requested by the sponsor's medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

10.5.2.2 Overdose of Docetaxel

Caution should be exercised to prevent inadvertent docetaxel overdose. An overdose of docetaxel will be defined as any dose administered that is ≥10% of the intended dose. There is no known antidote for docetaxel overdosage. In case of overdose, the subject should be kept in a specialized unit where vital functions can be closely monitored. Anticipated complications of overdosage include bone marrow suppression, peripheral neurotoxicity, and mucositis. Subjects should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken as needed.

10.5.2.3 Overdose of Pembrolizumab

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

10.5.2.4 Overdose of Cisplatin

There is no known antidote for cisplatin overdosage. Acute overdosage with cisplatin for injection may result in renal failure, hepatic failure, hearing loss, ocular toxicity, myelosuppression, nausea and vomiting, and neuritis. Management of overdosage should include general supportive measures including renal protection by IV hydration with or without the use of an osmotic diuretic. Refer to the local prescribing information for more details.

10.5.2.5 Overdose of Carboplatin

There is no known antidote for carboplatin overdosage. If overdose occurs, treatment may be needed for myelosuppression or hepatic toxicity. Refer to the local prescribing information for more details.

10.5.2.6 Overdose of Paclitaxel/Nab-paclitaxel

There is no known antidote for paclitaxel or nab-paclitaxel overdosage. Treatment should be directed at the primary anticipated toxicities, which consist of bone marrow suppression, peripheral neurotoxicity, and mucositis. Refer to the local prescribing information for more details.

10.5.2.7 Overdose of Pemetrexed

There is no known antidote for pemetrexed overdosage. Treatment should be directed at the primary anticipated toxicities, which consist of bone marrow suppression, infection with or without fever, diarrhea, and mucositis. Refer to the local prescribing information for more details.

10.5.3 Pregnancy

Pregnancy is not allowed in this trial. However, if any pregnancy occurs during trial participation, the pregnancy must be reported.

All reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor within 24 hours of knowledge of the event. In the case of pregnancy in the partner of a male subject, a separate ICF will be obtained from the female partner for collection of information regarding the pregnancy.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the trial and considered by the investigator as possibly related to trial treatment must be promptly reported to sponsor or designee.

Pregnant trial subjects must be withdrawn from treatment immediately, whereas male subjects may continue in the trial should pregnancy of female partners occur.

10.5.4 Regulatory Requirements for Suspected Unexpected Serious Adverse Reactions

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local regulatory authority and other regulatory agencies about the safety of the product under clinical investigation. Prompt notification of SAEs by the investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met (see Section 10.5.1).

The sponsor will ensure that all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) is documented and reported as soon as possible, but within a

maximum of 15 days (fatal or life-threatening SUSARs within a maximum of 7 days) of first knowledge by the sponsor or designee, to the competent regulatory authorities and/or to the ethics committee/IRBs according to the applicable local regulatory requirements. Relevant follow-up information of fatal or life-threatening SUSARs will be communicated subsequently the required reporting timelines. The sponsor will also communicate relevant information on SUSARs to the investigators at predefined periods according to local regulations.

The investigator should be aware of local reporting regulations to the IEC/IRB. The safety CRO will either supply the investigator with the reports which should be passed on to the IEC/IRB or report directly to the IEC/IRB, depending on local regulations.

The sponsor will notify all investigators of all SUSARs.

10.6 Follow-Up of Adverse Events and Serious Adverse Events

All AEs must be followed until they are resolved, or until the safety follow-up visit(s), or the start of new anti-cancer treatment, whichever comes first.

All SAEs and GEN1046-related AESIs qualifying for immediate reporting that are ongoing at the safety follow-up visit should continue to be followed on a regular basis, until the event has been resolved or until the investigator assesses it as chronic and all queries have been resolved.

Only SAEs judged by the investigator as related to trial treatment should be reported after the safety follow-up period.

10.7 Warnings and Precautions

No evidence available at the time of the approval of this trial protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided IB. Additional safety information collected between IB updates will be communicated in the form of investigator notifications. This information will be included in the ICF and should be discussed with the subject during the trial as needed.

10.8 Annual Safety Reporting by the Sponsor

The Sponsor will submit a single Annual Safety Report for GEN1046 as monotherapy and in combination with other anti-cancer drugs.

10.9 Data Monitoring Committee

A DMC will be established to ensure the continuing safety of the subjects enrolled in this trial. This committee will consist of at least 1 medical expert in the relevant therapeutic area; committee membership responsibilities, qualifications, and procedures will be documented in its charter.

10.10 Dose Escalation Committee and the Safety Committee

In addition to the DMC, subject safety will be monitored throughout the trial by the DEC and the sponsor SC. The DEC will be chaired by the sponsor medical monitor and membership will include at a minimum the trial principal investigators, members of the sponsor medical and safety departments, as well as additional staff as appropriate.

The DEC will meet regularly throughout the dose escalation. Dose escalation decisions will be proposed by the DEC in conjunction with the participating investigators. Timing of the dose escalation meetings will depend on the frequency of the DLT period and when a RP2D is determined.

The sponsor SC will convene after each DEC and/or DMC meeting. The sponsor SC will monitor all available treatment-emergent data to ensure subject safety. The sponsor SC is responsible for ensuring that participation in the trial is safe for trial subjects, evaluating the outcome of ongoing safety surveillance, evaluating outcomes of DMC meetings, performing benefit-risk assessments, and for ensuring that appropriate actions are taken when new safety issues emerge.

10.10.1.1 DEC for Expansion Cohort EC9 (Docetaxel Combination)

A DEC will meet regularly throughout the safety run-in for Cohort EC9, as described in Section 4.1.2.1.

10.10.1.2 DEC for Expansion Cohorts EC11A and EC11B (Pembrolizumab Combinations)

A DEC will evaluate all relevant safety data after the first 3 subjects have been treated and followed for a minimum of 3 weeks and after completion of the safety run-in, as described in detail in Section 4.1.2.2.

10.10.1.3 DEC and SC for Expansion Cohorts EC12 and EC13 (GEN1046 in Combination with Pembrolizumab and Platinum-based Chemotherapy Doublets)

A DEC and SC (see Section 10.10) will evaluate all relevant safety data as described in detail in Section 4.1.2.3.

11 STATISTICAL METHODS

All trial endpoints will be described using summary statistics. Time-to-event-endpoints (PFS, DoR, and OS) will be analyzed using Kaplan-Meier technique and censored in accordance with the FDA Guidance: "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics". Subjects not evaluable for objective response will be counted as non-responders. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented, and 25th and 75th percentiles may also be included as appropriate. Key data will be listed.

For statistical analyses and summaries, baseline is defined as the data available from the latest recorded measurement made before the first GEN1046 administration. Non-compartmental analysis estimates of PK parameters will be calculated and presented in the clinical trial report. Additional PK and PK/pharmacodynamic modeling will be performed and presented separately.

Details of statistical analysis and data reporting will be provided in a Statistical Analysis Plan (SAP) document finalized prior to database lock. Additional analyses may be added in the SAP and tables, listings, and figures shells will also be provided.

11.1 Analysis Sets

The Full Analysis Set (FAS), which consists of all subjects enrolled and treated with at least 1 dose of GEN1046, will be used for safety, efficacy, and the PK analyses. The per protocol set will not be applicable.

11.1.1 Dose-Determining Set

The Dose-Determining Set 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. This constitutes all evaluable subjects for the determination of MTD.

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.

11.2 Dose Escalation

11.2.1 mCRM

A 2-parameter BLRM guided by the EWOC principle will be used to make dose recommendations and estimate the MTD during the escalation phase of the trial.

For each available dose level, including intermediate doses (d=1,…,$n_{\text{max dose level}}$), the log odds of the DLT rate (π_d) is modeled as a function of standardized dose x_d (computed by dividing the median dose strength from each dose):

$$\theta_d = \log\left(\frac{\pi_d}{1-\pi_d}\right) = \alpha_0 + \alpha_1 \cdot x_d$$

For this trial a bivariate normal prior is placed on (α_0, log(α_1)), with α_0 marginally N(0, 3), log(α_1) marginally N(0.25, 0.5), and a correlation of 0. The prior was selected to achieve good operating characteristics for the scenarios described below.

EWOC: a dose level is considered to be safe to escalate to if there is at least a 40% probability that the DLT rate on the corresponding dose level during the DLT evaluation period is less than 30%. At any time during the trial, the method will not assign a subject to a dose that is not safe by this definition. If all dose levels are considered unsafe, the trial will stop early, with the MTD estimated to be below the experimental dose range.

11.3 Expansion

The expansion will be conducted using the Bayesian predictive probability of success (PPoS) approach with a maximum sample size of 40 per cohort for EC2 to EC8, EC10, EC12, and EC13, and a CCI [redacted]. EC1 may enroll up to 140 subjects if the benefit-risk assessment is favorable. In each cohort, the number of responders may be evaluated continuously after the first 10 treated subjects having sufficient data (either discontinued GEN1046 treatment or having at least 1 post-baseline imaging assessment) for objective response evaluation. The timing for the first efficacy analysis will be based on the latest time of either treatment discontinuation or meeting sufficient post-baseline imaging follow-up among the first 10 treated subjects, and the criterion for futility (PPoS <10%) will be used. See Section 11.13.2 for more details.

The docetaxel combination cohort (EC9) will follow the 6 + 6 design and be evaluated accordingly. A maximum sample size of 32 is planned for this cohort (see Section 4.1.2.1 for more details). EC11, EC12, and EC13 will have a safety run-in before expansion; see Section 4.1.2 for more details.

11.4 Subject Demographics and Baseline Characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for the FAS. Relevant medical histories and current medical history at baseline will be summarized by system organ class and preferred term.

11.5 Treatments

The safety set will be used for the analyses below.

The duration of exposure in months to trial drug as well as the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of trial treatment will be listed and summarized according to the anatomical therapeutic chemical classification system, by dose cohort.

11.6 Safety Analyses

Summaries for AEs will only include AEs that started or worsened during the on-treatment period, ie, the treatment-emergent AEs (TEAEs).

The incidence of TEAEs will be summarized by system organ class and/or preferred term, severity (CTCAE grade), type of AE, and relationship to GEN1046 and/or other components of trial treatment, as relevant.

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

All deaths (on-treatment and post-treatment) will be summarized.

All AEs, deaths, and SAEs (including those from the pre- and post-treatment periods) will be listed and those collected during the pretreatment and post-treatment period will be flagged.

Further summaries of AEs will be specified in the SAP.

See Section 4.1.1 for how the MTD will be determined.

11.6.1 Clinical Safety Data

Liver toxicity will be described separately as *a priori* this is the most relevant potential safety concern.

11.6.2 Laboratory Safety Data

For the analyses and reporting of the trial results, the central laboratory values will be used. All recorded local laboratory values will be listed.

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.

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

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades, if applicable, and the classifications relative to the laboratory normal ranges.
- 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.

- For laboratory tests where grades are not defined by the CTCAE:
  - Shift tables using the low/normal/high/(low and high) (or other project-specific) classification to compare baseline to the worst on-treatment value.

In addition to the above-mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the analysis plan.

11.6.3 Other Safety Data

ECG

12-lead ECGs including PR, QRS, QT, QTcF, and respiratory rate intervals will be obtained for each subject during the trial in accordance with the Schedule of Activities (Section 1.3).

Categorical analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced.

11.6.4 Safety Sensitivity Analysis

A sensitivity analysis will be performed for subjects in EC11, EC12 and EC13 in which AEs with onset 61 or more days after the last dose of GEN1046 are not considered. The rationale for this is to remove the impact of a potential long period where these subjects could be exposed to only trial medications other than GEN1046, CCI [redacted].

11.7 Vital Signs

Data on vital signs will be tabulated and listed; notable values will be flagged.

11.8 Pharmacokinetics

Individual curves of plasma concentration of each component of GEN1046 including information on actual dose, will be presented for all subjects. All available data will be shown in these figures. Concentrations below the lower limit of quantitation (LLOQ) will be set to LLOQ/2.

PK parameters (Table 11-1) will be calculated based on non-compartmental methods and will be calculated separately for Cycles 1 and 2 for dose escalation only.

The relation between derived PK parameters and covariates such as actual dose, weight and dose, and selected laboratory parameters will be evaluated graphically.

If deemed applicable compartmental modeling approaches to parameter estimation will be applied.

Further exploratory analyses of PK data may be performed.

Table 11-1 Non-compartmental Pharmacokinetic Parameters

Parameter	Description
CL	The total body clearance of drug from the plasma
V	Volume of distribution
AUC_{21days}	The AUC from time zero to day 21 (mass × time × volume-1)
AUC_{inf}	The AUC from time zero to infinity (mass × time × volume-1)
AUC_{last}	The AUC from time zero to last quantifiable measurement
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi-logarithmic concentration-time curve

AUC=area under the curve.

11.9 Immunogenicity Analyses

Titers of GEN1046 will be listed and positive/negative host immune response to GEN1046 and presence of neutralizing antibodies will be summarized (positive/negative). Presence of PK-concentrations above a certain threshold, that depends on the drug tolerance of the ADA assay, at the same time as the ADA sample may make the ADA undetectable and hence render non-conclusive. The association between positive/non-positive ADA and PK (pre-dose, AUC, C_{max}), major safety signals (CTCAE ≥ grade 3) and efficacy information (change in tumor size by CT scan) will be explored.

11.10 Efficacy Analyses

Efficacy analyses will be performed by trial phase and then by expansion cohort, and subgroup analyses based on tumor PD-L1 expression level may be conducted as an exploratory analysis. Analyses by PD-L1 expression will be based on the central testing results.

11.10.1 Anti-tumor Activity Based on RECIST 1.1

The RECIST criteria (v1.1) will be used to define response (Eisenhauer et al., 2009).

Table 11-2 Definition of Response (RECIST Criteria v1.1)

	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 LD of target lesions, taking as reference the baseline sum of LDs.
	Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of LDs while in trial. Follow-up measurements must have met the SD criteria at least once and for a minimum time period of 6 weeks (±7 days) after first treatment.
	Progressive Disease (PD)	≥20% (and ≥5 mm) increase in the sum of the LDs of target lesions, taking as reference the smallest sum of the target LDs 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.

LD=longest diameter; RECIST=Response Evaluation Criteria in Solid Tumors.

The BOR is the best response recorded from the start of the treatment until first documented disease progression. Subjects with CR or PR are considered to be objective response. Subjects with CR, PR, or SD are considered to be in disease control. Subjects with NE are counted as non-responders.

The best change (maximal reduction in the sum of the diameters in the target lesions) in target lesions at any time on trial will be reported using waterfall plots.

Individual subject data listings and summaries of objective response, best overall tumor response and disease control will be presented by dose cohort/indication and total.

11.10.2 Duration of Response

DoR only applies to subjects whose confirmed BOR is CR or PR and is defined as the time from the first documentation of objective tumor response (CR or PR) to the date of first PD or death due to any cause.

DoR will be censored and summarized in the same way as PFS.

11.10.3 Progression-Free Survival

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

PFS will be censored if no PFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-neoplastic therapy. PFS will also be censored at this date in the case of a PFS event following 2 or more missed visits in accordance with the FDA guideline on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

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 product limit algorithm will be presented. The 2-sided 95% confidence interval will be presented as well.

11.10.4 Overall Survival

OS is defined as the number of days from Day 1 in Cycle 1 to death due to any cause. If a subject is not known to have died, 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.

11.10.5 Anti-tumor Activity Based on iRECIST

Responses assigned using iRECIST (Seymour et al., 2017) have a prefix of "i" eg, "immune:" iCR or iPR, and unconfirmed PD (iUPD) or iCPD to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for iSD, progression-free-survival (iPFS), duration of response (iDoR), 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, eg, iORR should be analyzed and reported in the same way as ORR; see Section 11.10 above for details.

If too few additional responders after initial PD are observed, this exploratory analysis may be omitted.

11.10.6 Efficacy sensitivity analysis

Sensitivity analyses will be performed to address the impact of subjects in EC11, EC12 and EC13 being on treatment with components of the treatment regimen other than GEN1046, following the recommendation in protocol amendment 10.0 CCI [redacted] (see Section 4.1.2 and Section 8.1 for details on the recommendation). Sensitivity analyses will be conducted for ORR, DoR, PFS and OS. For ORR, data collected after 60 days from last dose of GEN1046 will be disregarded in the determination of BOR. For DoR, PFS, and OS, censoring will be applied at the end of a 60-day follow up period from last dose of GEN1046.

11.11 Biomarker Analyses

Retrospective biomarker analyses in this trial are exploratory and focused on confirming the MoA of GEN1046, identifying potential pharmacodynamic markers to help identify the appropriate dose and schedule of GEN1046, and identifying potential predictive markers that may be further validated in prospective trials with GEN1046.

Biomarkers, such as PD-L1 and 4-1BB expression, peripheral immune cell populations, and cytokine measurements will be tabulated for all subjects who had samples collected and testing performed. Biomarker assessments will be summarized by time point using descriptive statistics. Changes in biomarker parameters, as compared to baseline, will be calculated and analyzed for

association with relevant clinical endpoints such as objectives response, PFS, OS. Subgroup analysis may be performed to evaluate differences between biomarker parameters in groups of responders and non-responders or other clinically relevant subgroups, and to evaluate the associations between biomarker parameters and specific clinical endpoints. Univariate and multivariate analyses, as well as pathway analyses may also be performed if applicable. Any pharmacodynamic measures will be listed, tabulated, and plotted as appropriate. Subjects may be grouped by cohort, dose schedule, or clinical response.
Results of biomarker analyses may be presented in a separate report.

11.12 Planned Analyses

11.12.1 Interim Futility Analyses

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.
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 SOC (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 11-3), the data indicate that it is unlikely the ORR will be better than the response rate of current SOC 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 11-3 PPoS Operating Characteristics in the First 10 Subjects for EC1 Through 7, EC10

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.

Table 11-4 summarizes the operating characteristics of the interim analysis of CCI . The benchmark ORR for CCI (1L non-squamous NSCLC; based on the Keynote-189 trial) is 41% for subjects treated with pembrolizumab and chemotherapy combination with TPS <50%. The benchmark ORR for CCI (1L squamous NSCLC; based on the Keynote-407 trial) is 57% for subjects treated with pembrolizumab and chemotherapy combination with TPS <50% (Gandhi et al., 2018; Paz-Ares et al., 2018). CCI

Table 11-4 PPoS Operating Characteristics in the First 10 Subjects for CCI

			Initial Interim Analysis (n=10)		Initial Interim Analysis (n=20)		Final Analysis (n=40)
p_0	**p_1**	**True ORR**	**Futility limit (# of responders)**	**Pr(Futility)**	**Futility limit (# of responders)**	**Pr(Futility)**	**Pr(obs ORR ≥ p_1%)**
41%	61%	41%	2	15%	7	22%	<1%
		46%	2	9%	7	11%	3%
		51%	2	5%	7	5%	10%
		56%	2	2%	7	2%	25%
		61%	2	1%	7	<1%	49%
57%	77%	57%	4	8%	10	19%	1%
		62%	4	4%	10	9%	3%
		67%	4	2%	10	4%	11%
		72%	4	1%	10	1%	28%
		77%	4	<1%	10	<1%	56%

obs=observed; ORR=objective response rate; PPoS=predicted probability of success; Pr=probability; p_0 reflects the response rate of the current standard of care.

The operating characteristics of the design were based on 40,000 simulation runs. If the true ORR is close to p_0, there is reasonable chance to reach the futility criteria at interim. On the other hand, if the true ORR is close to p_1 or higher, the probability to stop for futility is very low. The predictive probabilities 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.

11.12.1.1 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.

The SAP will describe the planned interim analyses in greater detail.

Table 11-5 Operating Characteristics of the Predictive Probability Design

			Interim Analysis 1 (n=10)		**Interim Analysis 2 (n=20)**	
p_0	p_1	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%

p_0 reflects the response rate of the current standard of care.
n=number of subjects; ORR=objective response rate; p_1=ORR that warrants further evaluation of the drug; Pr(Futility)=probability of futility.

Table 11-6 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.

11.12.2 Primary Analysis

The primary analysis will be conducted after the primary analysis cutoff date which will be shortly after all subjects have discontinued the trial or 1 year after the first dose of the last subject enrolled (whichever occurs first). At this time, a survival sweep will be performed to determine the survival status of all remaining subjects in the trial.

11.12.3 Final Analysis

A final analysis will be conducted after the end of trial (see Section 4.5.2). A final survival sweep will be performed to determine the survival status of all remaining subjects in the trial.

11.13 Sample Size Estimation

11.13.1 Dose Escalation

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

11.13.2 Expansion

Each expansion cohort from cohorts EC2 to EC7 and EC10 may enroll up to 40 subjects. EC1 may enroll up to 140 subjects. EC8 may enroll approximately 40 subjects. EC9, the docetaxel combination cohort, may enroll up to 32 subjects. EC11, the pembrolizumab combination cohort, may enroll up to 40 subjects with the possibility of expansion to 80 subjects in total if encouraging efficacy is observed. EC12 and EC13, the pembrolizumab and platinum-based chemotherapy doublets combination cohorts, may enroll up to 80 subjects in total (40 in each cohort, including safety run-in). The 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.

12 DATA HANDLING AND RECORD KEEPING

12.1 Source Documentation

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly documented at the trial site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial, described in the monitoring guidelines (or equivalent), and captured in a source data verification log at site.

For each subject, the investigator must indicate in the hospital/medical source records that the subject participates in this trial and the date of obtaining the ICF. The records should document data on the condition of the subject at the time the subject is enrolled in the trial to enable verification of eligibility. Signed and dated ICFs will be stored and archived according to local requirements. In addition, the following information, at the minimum, will also be recorded in the hospital/medical source records for each subject:

- Subject's name and date of birth.
- Screening/randomization number.
- Trial identification.
- Confirmation of eligibility for participation in the trial**,** including diagnosis.
- Medical history.
- Date of each visit.
- Any assessment performed eg, results of safety and efficacy evaluations.
- Concomitant medications.
- Occurrence of any AEs/SAEs (including description and duration).
- Status of the subject at the end of trial.
- Reason for discontinuation/withdrawal, if applicable.

Any worksheets used to capture data to facilitate completion of the eCRF will become part of the subject's source documentation. In addition to the source data in medical records, data may be recorded directly electronically (eg, ECGs, patient reported outcomes, etc). Such data are considered source data, and are accessible by both the investigator and sponsor.

The author of an entry in the source should be identifiable.

Information included in the subject's hospital records may be subject to local regulations. If there is a discrepancy between local requirements and the protocol, local regulations should be followed.

12.2 Case Report Form Completion

CRF data will be transcribed into an EDC system by trial-site personnel from the source documents. Both EDC and other electronically captured trial data are transmitted in a secure manner to the sponsor within agreed upon timeframes.

Data relating to the trial must be documented and reported in English. Trial site personnel must complete the CRF as soon as possible after the data are available and preferably within 5 days. Source data and the CRFs should be available for review at the next scheduled monitoring visit.

All eCRF entries, response to queries, corrections, and alterations must be made by the investigator or other authorized trial-site personnel. The completed eCRF must be verified and approved by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form.

Corrections to the eCRF after the initial data entry can be done as follows:

- Trial-site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool).
- The monitor can generate a query for resolution by the trial-site personnel.
- The sponsor or designee can generate a query for resolution by trial-site personnel.

12.3 Data Quality Management

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and trial-site personnel before the trial, periodic monitoring visits by the sponsor (or the sponsor's delegate) and direct transmission of clinical laboratory data from a central laboratory, ECG data from ECG vendor and CT/MRI scans and reads from the central imaging vendor (expansion only, applicable prior to Protocol Amendment 11) into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided. The sponsor/CRO will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the trial database they will be verified for accuracy and consistency with the data sources.

12.4 Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs and all source documents, as well as a source document location list, that support the data collected from each subject, as well as all trial documents as specified in ICH/GCP guideline Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for 25 years after end of trial. These documents will be retained for a longer period if required by the applicable regulatory requirements. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a person who will

accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this trial, the investigator/institution must permit access to such reports.

13 ETHICS

13.1 Trial-Specific Design Considerations

Thorough scientific evaluation of any promising treatment before market authorization is an ethical requirement. In the continuing search for medications with improved efficacy and safety profiles, it is necessary to fully investigate and understand new products before public exposure.

This trial is being conducted to evaluate the multiple-dose PK of GEN1046 in subjects with malignant solid tumors. The results of this trial will provide useful information on the PK of GEN1046. These data are also needed to assist in developing dosage adjustment guidance for future trials.

As with all clinical and PK trials, there are risks associated with venipuncture and multiple blood sample collection. To avoid multiple venipunctures, which cause additional discomfort and other potentially toxic effects, the use of IV indwelling catheters is permitted in this trial. The blood sample collection scheme was designed to collect the minimum number of blood samples that accurately and completely describe the PK of GEN1046.

Potential subjects will be fully informed of the risks and requirements of the trial and, during the trial, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the trial is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the trial, and provide their consent voluntarily will be enrolled.

13.1.1 Trial and Site Start and Closure

The first act of recruitment is the first subject screening visit and will be the trial start date.

The sponsor reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

In addition, the investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given to the sponsor in advance of the intended termination.
Reasons for the early closure of a trial site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's guidance documents/trial plans, ICH GCP E6(R2), and applicable regulatory requirements.
- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further trial drug development.

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

13.2 Regulatory Ethics Compliance

13.2.1 Regulatory and Ethical Considerations

The principles of the Declaration of Helsinki, the consolidated ICH-GCP, and applicable regulations and national law(s) (eg, 21 CFR and European regulation 536/2014 for clinical trials) in the country(ies) where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

ICH GCP E6(R2) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the trial data are credible.

13.2.2 Investigator Responsibilities

The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, ICH GCP E6(R2), and applicable regulatory and country-specific requirements. This includes supervision of the trial and staff. Delegation of responsibilities should be to only qualified staff and should be documented. In case the investigator is unavailable (eg, on vacation), the investigator should assure that a qualified, trained deputy physician is available for medical care of the subjects. Handover of information must be ensured and documented. The investigator shall notify the sponsor of any serious breach of ICH GCP E6(R2), the protocol, or any regulation where required immediately.

13.2.2.1 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

13.2.3 Independent Ethics Committee or Institutional Review Board

This trial will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments to the protocol (if applicable), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this written approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or trial conduct), the amendment and applicable ICF revisions

must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

The IB and updates to the IB, unexpected SAEs where a causal relationship cannot be ruled out, serious breaches, serious non-compliance, annual written summaries of the trial status and deviations to the protocol implemented to eliminate immediate hazards to the subjects must be submitted to the IEC/IRB.

Interim reports on the trial and/or reviews of trial progress will be submitted by the investigator, where applicable, to the IEC/IRB at intervals stipulated in the IEC/IRB guidelines.

At the end of the trial, the investigator (or sponsor where required) will notify the IEC/IRB about the trial completion.

13.2.4 Informed Consent Process

The ICF(s) that is/are used must be approved by the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The ICF should be in accordance with principles that originated in the Declaration of Helsinki, ICH GCP E6(R2), applicable regulatory requirements, and sponsor policy.

It is the personal responsibility of the investigator or an authorized member of the trial-site personnel to explain to potential subjects (or their legally acceptable representatives) the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail.

Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time without justifying the reason. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of their disease. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations.

By signing the ICF, the subject (or legally authorized representative) is authorizing such access, and agrees to allow their trial physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject (or his/her legally acceptable representatives) will be given sufficient time to read the ICF and the opportunity to inquire about details of the trial prior to deciding whether to participate in the trial. After this explanation and before any trial-specific procedure is performed, consent should be appropriately recorded by means of either the subject's or their legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

The subject (or his/her legally authorized representative) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, the US Health Insurance Portability and Accountability Act and EU General Data Protection Regulation requirements, where applicable, and the IRB/IEC or trial center. The investigator or

authorized person obtaining the informed consent must also sign and date the ICF. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject (or legally acceptable representative) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject (or legally acceptable representative) is obtained.

A subject who is rescreened is not required to sign another ICF unless the subject's rights, risks regarding trial participation, or well-being has changed since the first ICF was obtained.

A separate ICF will be used for the required DNA/RNA research component of the trial if required by local regulations.

13.2.5 Data Protection

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF or any other documents submitted to the sponsor/sponsor's representative, the subjects will not be identified by their names, but by an identification code, which consists of an assigned number in the trial. The confidential subject identification code and the signed Informed Consent Documents will be maintained by the investigator in strict confidence.

In relation to the collection and handling of data, including any personal data, potential risks to the subjects have been assessed and adequate technical and organizational measures are implemented to ensure a level of security appropriate to the risk. The security measures implemented entail among other things that:

- Access to data has been restricted so that access is only granted to authorized individuals.
- Data is only stored on IT systems and networks that are protected against virus, malware, and unauthorized access.
- Data is backed up at regular intervals. In case of a data breach, a clear allocation of roles and responsibilities for managing the data breach, including notifying affected subjects and authorities, has been established in order to mitigate any adverse impact on the subjects.

Additional technical security measures implemented include that:

- All data is encrypted when at rest.
- Data has been pseudonymized to the effect that only authorized individuals can link data to identified individuals.
- A data breach response plan has been established.

The collection and processing of personal data from subjects enrolled in this trial will be limited to those data that are necessary to fulfill the objectives and purposes of the trial and as specifically defined in the protocol.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate

technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place, as detailed above. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent or description of other legal basis for the processing of personal data for the purpose of the trial and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for trial-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries, as specified in the ICF.

The subject has the right to request access to their personal data and the right to request rectification of any data that are not correct or complete, by contacting the investigator. Reasonable steps will be taken by the investigator to respond to a request, taking into consideration the nature of the request, the conditions of the trial, the clinical trial agreement including any other relevant agreement, and applicable laws and regulations. The investigator will inform and work together with the sponsor when handling such requests.

In case of a potential data breach of the personal data, the investigator will inform the sponsor immediately and will contain the breach from spreading, where possible. Investigator and sponsor will work together to assess the risk to the individuals concerned, based on the circumstances of the case, including which data were involved, what security measures were in place (for instance, if the data was encrypted or pseudonymized), and who might have accessed the data, etc.

Based on this assessment, the data breach might be reported to the relevant authorities and/or the individuals concerned. Mitigating actions will be taken to avoid this event from reoccurring.

13.2.6 Dissemination of Clinical Trial Data

The protocol information will be registered in a publicly accessible database (eg, clinicaltrials.gov, EU CTIS, and/or other national registries/health authority websites). In addition, after trial completion (defined in Section 4.5.2) and finalization of the CSR, the results of this trial will be submitted for disclosure and posted in a publicly accessible database of clinical trial results as required by local regulations (eg, clinicaltrials.gov, EU CTIS).

Exploratory biomarker research is not conducted under standards appropriate for the return of data to subjects or investigators. In addition, the sponsor cannot make decisions as to the clinical significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

13.2.7 Long-Term Retention of Samples for Additional Future Analyses

Biomarker research is focused on evaluating the biology of GEN1046 or the disease of interest. In order to understand which subjects may respond best to the therapy based on emerging scientific evidence relating to a potential correlation between a biomarker and treatment efficacy and/or safety, the sponsor may perform additional research on remaining samples during the

clinical trial or for a period of 5 years after the last subject's last treatment for a retrospective analysis. In this case, such analyses would be specific to research related to the trial drug or diseases being investigated by the sponsor.

14 ADMINISTRATIVE PROCEDURES

14.1 Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. Approval must be obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in the sponsor's medical monitor or contact information). Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a deviation from the protocol is unavoidable, the investigator or other physician in attendance will contact the sponsor (see the separate sponsor contact information page, which is provided separately from the protocol). Except in emergency situations, this contact should be made before implementing any deviations from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data documented in the eCRF and source documents will reflect any deviation from the protocol, and the source documents will describe this departure and the circumstances requiring it.

14.2 Regulatory Documentation

14.2.1 Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, in accordance with local regulations. A trial may not be initiated until all local regulatory requirements are met.

14.3 Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification log to permit easy identification of each subject during and after the trial. This document will be reviewed by the sponsor trial-site contact for completeness.

The subject identification log will be treated as confidential and will be filed by the investigator in the Investigator Site file and will never be transferred to the sponsor or any third parties. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the trial will identify subjects by their subject number (or screening number if not enrolled).

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the trial.

14.4 Monitoring

The sponsor will use a combination of remote and on-site monitoring to monitor this trial.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial site visit log that will be kept at the trial site. The first post-initiation visit will be made as soon as possible after enrollment (ie, the first subject has

signed the ICF) has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and trial-site personnel and are accessible for verification by the sponsor trial-site contact. If electronic records are maintained at the trial site, the method of verification must be discussed with the trial-site personnel. Where allowed in accordance with local regulations, eg, in the event of a national emergency, and in agreement with the investigator, remote source data verification or source data review may be performed.

The investigator must permit the monitor access to all source data, including electronic medical records and/or documents for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the trial-site personnel. The sponsor expects that, during monitoring visits, the relevant trial-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of trial-related documents. The monitor will meet/talk with the investigator on a regular basis during the trial to provide feedback on the trial conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, trial-site personnel will be available to provide an update on the progress of the trial at the site.

14.5 On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the trial site at any time during or after completion of the trial to conduct an audit of the trial in compliance with regulatory guidelines and company policy. These audits will require access to all trial records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The principal investigator and trial-site personnel are responsible for being present and available for consultation during routinely scheduled trial-site audit visits conducted by the sponsor or its designees.

Similar procedures for inspections may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection. Regulatory Inspectors must be allowed direct access to original medical records (source data/documents).

14.6 Publication

All information, including but not limited to information regarding GEN1046 or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory or biomarker research data, generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this trial, and will not use it for other purposes without the sponsor's prior written consent. CROs involved in the trial are not permitted to publish without the sponsor's prior written approval.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of GEN1046, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical trials to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

The results of the trial will be reported in a CSR generated by the sponsor and will contain data from all trial sites that participated in the trial. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the trial will be used to determine a coordinating investigator for the CSR (eg, when a signature by a coordinating investigator is required). Results of exploratory biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR. Trial subject identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines (Battisti et al., 2015; ICMJE, 2010; ICMJE, 2016; ICMJE, 2019), the sponsor in conjunction with any collaborative group(s), shall have the right to publish such primary (multicenter) data and information as per the pre-specified and approved publication plan. If an investigator wishes to publish information from the trial, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter trial designs and sub-trial approaches, secondary results generally should not be published before the primary endpoints of a trial have been published. Similarly, investigators will recognize the integrity of a multicenter trial by not submitting for publication data derived from the individual trial site until the combined results from the completed trial have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter trial publication.

Authorship of publications resulting from this trial will be based on the guidelines on authorship, such as those described in the current version of “Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals” (ICMJE Recommendations) http://www.icmje.org/recommendations/), which state that the named authors must have made a significant contribution to the design of the trial or analysis and interpretation of the data, provided critical review of the paper, given final approval of the final version, and agreed to be accountable for all aspects of the work (ICMJE, 2010).

14.7 Liabilities and Insurance

The sponsor is responsible for taking out relevant clinical trial insurance in accordance with local law and regulations.

15 LAY PROTOCOL SYNOPSIS

NOTE: The lay protocol synopsis supports public disclosure activities and is not meant for site/investigator use.

Protocol Title	First-in-human, Open-label, Dose-escalation Trial With Expansion Cohorts to Evaluate Safety of GEN1046 in Subjects With Malignant Solid Tumors	
Brief Title	GEN1046 Safety Trial in Patients With Malignant Solid Tumors	
Protocol Number	GCT1046-01	
Compound	Acasunlimab (GEN1046; DuoBody®-PD-L1×4-1BB)	
Regulatory Agency Identifier Number(s)	**EU CT No.**	2023-509059-15-00
	NCT No.	NCT03917381

Brief Summary

The goal of this trial is to learn about the antibody GEN1046 when it is used alone and when it is used together with standard of care treatment (docetaxel) or another antibody cancer drug, pembrolizumab (with or without chemotherapy), for treatment of patients with certain types of cancer. All subjects will receive active drug; no one will receive placebo.

This trial has 2 parts. The purpose of the first part is to find out if GEN1046 is safe and to find out the best doses of GEN1046 to use. The purpose of the second part is to give GEN1046 to more subjects to see how well the doses of GEN1046 selected in the first part work against cancer when given alone and how well they work when given with pembrolizumab (with or without other chemotherapy) or docetaxel.

Trial details include:

- The average trial duration for an individual subject will be about 74 weeks.
- The average treatment duration for an individual subject will be about 21 weeks.
- The visit frequency will be weekly at first and lessening over time until visits are only once every 3 weeks.

Intervention

Subjects in this trial will receive the below treatment once every 3 or 6 weeks, depending on which treatment they are assigned to:

- GEN1046 alone (100 mg or 500 mg into the vein [IV]) or
- GEN1046 with docetaxel (55 mg/m^2 or 75 mg/m^2 IV) or
- GEN1046 with pembrolizumab (200 or 400 mg IV) or
- GEN1046 with pembrolizumab and chemotherapy (described below)
  - chemotherapy: pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 OR carboplatin AUC 5 mg/mL/min once every 3 weeks
  - chemotherapy: carboplatin AUC 6 mg/mL/min IV once every three weeks plus paclitaxel 200 mg/m^2 once every three weeks OR nab-paclitaxel 100 mg/m^2 once every week

All subjects will receive active drug; no one will receive placebo.

Rationale

The purpose of this study is to determine the severity of the possible side effects and the potential added benefit of treatment with GEN1046 alone and in combination with docetaxel or pembrolizumab (with or without chemotherapy) in patients with certain types of cancer.

GEN1046, also known as DuoBody®-PD-L1x4-1BB, is an antibody that can bind to 2 different molecules that are present on many cells involved in cancer. GEN1046 has been investigated in other clinical studies in different solid tumors but it is not yet approved for treatment of cancer. The type of immunotherapy treatment known as checkpoint-inhibitors, for example pembrolizumab, have been approved as treatment for patients with certain cancers. Docetaxel is commonly used as a standard-of-care treatment for certain types of lung cancer which have spread to other parts of the body.

Objectives (Purpose) / Endpoints (Assessments)	
Primary Objective(s)	***Primary Endpoint(s)***
• Determine the dose of GEN1046 to be studied in the second part of the trial • Determine if GEN1046 is safe	• How often "dose-limiting toxicities" (DLTs) occur, which are a specific type of side effect that guide investigators about what doses to test next • How often side effects occur and how serious they are and how often laboratory values are outside the normal range and by how much
Secondary Objective(s)	***Secondary Endpoints(s)***
• Determine if GEN1046 is safe when combined with docetaxel or pembrolizumab (with or without chemotherapy) • Evaluate how the body handles GEN1046 • Evaluate if the body reacts to GEN1046 • Evaluate how the tumor is affected	• How often side effects occur and how serious they are and how often laboratory values are outside the normal range and by how much • Amount of GEN1046 in the blood and how the amount changes over time • Does the body create antibodies that target GEN1046 • Objective response rate (a measurement of how the tumor has reacted [shrinkage or growth] to treatment) • Disease control rate (the percentage of subjects who obtained either tumor shrinkage or stopping of the tumor growth during the treatment) • Duration of response (the time period with tumor shrinkage before the growth starts again)
Trial Population In Part 1: Subjects with various cancers for which there is no available treatment, 18 years of age or older. In Part 2: Subjects with non-small-cell lung cancer [NSCLC], urothelial carcinoma (UC), endometrial cancer, triple-negative breast cancer (TNBC), squamous cell carcinoma of the head and neck (SCCHN), or cervical cancer, 18 years of age or older.	
Ethical Considerations Results from studies have suggested antitumor activity of GEN1046 in subjects with various incurable cancer types. Other research suggests that GEN1046 may also work together with other cancer drugs, such as docetaxel or pembrolizumab with chemotherapy, Importantly, clinical research studies with GEN1046 have shown manageable serious risks or lasting side effects in subjects. Additionally, studies with the combination of GEN1046 and pembrolizumab showed to be safe for subjects with incurable cancer other than NSCLC. Based on all available results to date, the possible benefits of treatment with GEN1046 and docetaxel or pembrolizumab (with or without chemotherapy) outweigh the risks. All of the tests and procedures performed throughout the trial are being done to confirm the combination of GEN1046 with docetaxel or pembrolizumab (with and without chemotherapy) is both safe and effective (that is, the drugs have antitumor activity), while ensuring the well-being of subjects is closely monitored.	

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17 APPENDICES

Appendix 1 Definition of Reproductive Potential and Contraception

In this trial, subjects are considered to have reproductive potential, UNLESS they are postmenopausal or permanently sterile.

- A postmenopausal state is defined as no menses, in subjects >45 years of age, for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in subjects not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

All female subjects must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 6 months after receiving the last dose of GEN1046.

Female subjects of reproductive potential must agree to use adequate contraception during and for 6 months after the last GEN1046 administration. Adequate contraception is defined as highly effective methods of contraception (Table 17-1). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year, when used consistently and correctly.

Table 17-1 Highly Effective Methods of Contraception

• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  • Oral
  • Intravaginal
  • Transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  • Oral
  • Injectable
  • Implantable[2]
• Intrauterine device[2]
• Intrauterine hormone-releasing system[2]
• Bilateral tubal occlusion[2]
• Vasectomized partner[2, 3]
• Sexual abstinence[4]	

1	Hormonal contraception may be susceptible to interaction with GEN1046, which may reduce the efficacy of the contraception method.
2	Contraception methods that, in the context of this guidance, are considered to have low user dependency.
3	Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success.
4	In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Table adapted from 'Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1.' (CTFG, 2020).

Appendix 2 Bayesian Dose Escalation Design for a Phase I Trial of a Single-Agent Antibody Therapeutic

Bayesian Dose Escalation Design for GEN1046

Submitted to Genmab
By Berry Consultants, LLC
August 31, 2018

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1 Introduction

This is a phase I dose escalation study to characterize the dose-toxicity relationship and to estimate the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) for GEN1046. The MTD will be the highest safe dose that has an estimated dose limiting toxicity (DLT) rate below 30%.

Dose escalation will be conducted according to a continual reassessment method (CRM) algorithm with overdose control. The defining property of a CRM is a model relating dose to the probability of a DLT. The CRM chooses the dose for the next cohort by estimating the MTD with the currently available data, and then selecting a dose that is as close to the MTD as possible while obeying certain constraints (such as not escalating too fast).

After each cohort of patients are assessed for a DLT during the DLT period, the model parameters will be updated and a next dose suggested based on the posterior probability of DLT at each dose.

The doses will include 7 main dose levels: 25, 80, 200, 400, 800, 1200, 1600 mg, as well as several intermediate doses of 50, 140, 300, 600, 1000, and 1400 mg. The intermediate doses may be skipped if appropriate per the dose-toxicity model.

The study will enroll a maximum of 50 patients to the dose escalation.

The dose escalation begins with an accelerated phase consisting of single-patient cohorts. Upon the first instance of a Grade 2 toxicity (that meets the definition in the protocol) or DLT, the cohort size will expand to 3 patients.

2 Statistical Modeling

2.1 Dose-Toxicity Model

For each available dose, including intermediate doses ($d = 1....13$), we model the DLT rate (π_d) on the log odds scale

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$$\theta_d = \log\left(\frac{\pi_d}{1-\pi_d}\right).$$

We use a two parameter model relating the log odds to standardized doses x_d,

$$\theta_d = \alpha_0 + \alpha_1 x_d,$$

where the standardized dose is computed by taking the natural logarithm of the dose strength divided by the median dose strength for each dose, as shown in Table 1 below. The main doses are indicated by an asterisk in the table. We place prior distributions on each of the α terms and after each cohort is treated and assessed for DLT, the distributions of these parameters are updated, resulting in a posterior distribution used to estimate the MTD and select the dose for the next cohort.

Table 1 Actual and Standardized Doses (Used in Statistical Modeling)

Dose Level (d)	Dose (mg)	Standardized Dose (x_d)
1*	25	−2.773
2	50	−2.079
3*	80	−1.609
4	140	−1.050
5*	200	−0.693
6	300	−0.288
7*	400	0.000
8	600	0.405
9*	800	0.693
10	1000	0.916
11*	1200	1.099
12	1400	1.253
13*	1600	1.386

For this trial we place a bivariate normal prior on $(\alpha_0, \log(\alpha_1))$, with α_0 marginally $N(0,3)$, $\log(\alpha_1)$ marginally $N(0.25,0.5)$, and a correlation of 0. The prior was selected to achieve good operating characteristics for the scenarios described below. Generally, the prior anticipates the lower doses have a good chance of being safe while the higher doses are a priori likely to be unsafe. However, the prior is generally weak. Thus, data indicating high doses are safe will still result in escalation.

2.2 Safety Definition

Each dosing frequency will be continuously monitored for safety. We define a dose level as safe if there is at least a 40% probability that the DLT rate is less than 30%. That is,

$$\Pr(\pi_d < 30\%) > 40\%.$$

At any time during the trial, a patient cannot be assigned to a dose that is not safe by this definition. If all dose levels are considered unsafe, the trial will stop early, with the MTD estimated to be below the experimental dose range.

2.3 Definition of the Maximum Tolerated Dose

The MTD will be the dose that has an estimated DLT rate nearest to 30% and that is also considered safe by the above definition.

3 Dose Escalation and Stopping Rules

3.1 Starting Dose and Entry Into the Study

The starting dose will be 25 mg.

Subjects will be enrolled within cohorts, beginning with single-patient cohorts, then expanding to larger (3 patient) cohorts. Once the cohort is filled, enrollment to the study will pause while DLTs are assessed. Once all subjects within a cohort have been assessed for a DLT during the DLT period, enrollment will open to a newly selected dose based on the DLT model recommendation, subject to the escalation constraints described below.

3.2 Assignment of Dose Level (Escalation constraints)

The dose-toxicity model will be used to assign patients to doses. However, assignment of dose level is also governed by additional rules.

At no time may subjects be enrolled on a dose that is considered unsafe (see definition above).

At the beginning of the trial, cohorts are of size 1 until either a DLT is observed OR until a protocol-defined Grade 2 toxicity is observed, at which point cohorts will be of size 3.

After the initial single-patient cohort run-in, after each cohort the model is fit and the DLT probabilities are estimated for each dose. The MTD is the highest dose that has an estimated Pr(DLT) below 0.30 that is also safe.

For future allocations, the CRM will attempt to allocate patients at the MTD. However, to prevent escalation that is too rapid, we impose the following constraints:

- The maximum escalation increment between cohorts is two dose levels (e.g. 1 main dose level, skipping the intermediate doses). If the model estimates

the MTD to be more than two dose levels above the most recent dose allocated, the CRM will restrict escalation and only escalate two dose levels.
- The model may deescalate to any degree (but re-escalation is restricted per the rules above)

3.3 Stopping the Dose Escalation

The dose escalation will stop when any of the following conditions are met

1) The maximum number of patients has been enrolled (N = 50)
2) No doses are considered safe
3) The recommended MTD already has been allocated at least 9 patients. Instead of continuing, the CRM considers this adequate evidence to stop the escalation rather than continue to accrue more patients at the same level.

After the escalation stops, the MTD is defined as the dose with Pr(DLT) (estimated by the Bayesian posterior mean) closest to 0.30 which satisfies the safety criteria of $\Pr(\pi_d < 30\%) > 40\%$.

4 Example Trials

The individual pages of each file show the results after each cohort is enrolled. The first panel of each page shows the data after that cohort is complete, with the x-axis providing the patient id, the y-axis showing the assigned dose, and either black circles (no DLT), a pink dot (Grade 2) or a red triangle (DLT) is used to denote the result for that patient. Thus, the first panel as a movie displays the dose assignments throughout the trial and the observed data. The second panel on each page shows the current model based fitted probabilities of a DLT for each dose (solid black line) along with 95% credible intervals. These fitted probabilities are obtained by taking the observed data (first panel) and combining it with the prior distribution to produce a posterior distribution for the logistic regression parameters. The mean of that posterior distribution for each dose results in the black curve in the second panel. The threshold value of 0.30 is shown in the second panel of each page with a horizontal line. In the third panel, the height of each bar indicates the probability each dose is has DLT rate above 0.30, which incorporates not only the posterior mean but also the variation in the posterior distribution. The bars are color-coded so that blue indicates a safe dose, and red indicates unsafe.

As the trial continues, the estimated MTD at each step is printed at the bottom of the second plot, in red font. The estimated MTD is the highest dose that maintains less than a 30% fitted DLT rate and is also considered safe.

Of particular interest is the trial behavior in the absence of DLT. The trial begins with single-patient cohorts, escalating quickly in increments of two dose levels (skipping intermediate doses) as long as those dose levels are considered safe and not above the model-estimated MTD. At the first occurrence of Grade 2 toxicity or DLT, intermediate dose levels may be explored. Skipping the intermediate doses is consequence of both the design (which enables jumps of 2 dose levels) and the model fit, including prior specification.

Also of note is the trial behavior when dealing with early DLTs. Currently, if 2 DLTs are observed out of 3 patients at the 25 mg dose, the trial terminates. Thus, the shortest possible trial has 3 patients, and would consist of 3 patients on the lowest dose, with 2 DLTs.

If a DLT is observed in the first single patient cohort and then two new patients at that dose do NOT have a DLT, the trial will add an additional cohort to the first dose.

5 Simulations and Operating Characteristics

5.1 Scenarios of interest

We evaluate the proposed design by simulation. Thus, we hypothesize several possible underlying truths of the dose-toxicity curve, and determine how the trial will behave in each of those scenarios. For example, if all the doses were toxic, we would want the trial to stop as soon as possible and recognize all doses are unsafe. If the smaller doses are safe and 200mg is in fact the MTD, we would like the algorithm to identify a dose around 200mg as the MTD as much as possible. The same design ideally can handle all the different scenarios. Note this ideal is difficult to achieve in practice with any phase 1 design due the small sample sizes typically employed.

We consider the following possible scenarios. The MTD in the shaded cell is the highest dose with DLT rate below 0.30. These scenarios span a range of possible MTDs and shapes.

Figure 1 shows the scenarios graphically. The red line indicates the probability of a DLT and the pink line indicates the probability of a Grade 2 or higher toxicity. The data for Grade 2 toxicity is simulated only to act as a trigger for expanding from single-patient cohorts to 3 patient cohorts. Only DLTs are included in the dose-toxicity model. The pink lines are shifted left relative to the red curves by applying an offset of 1 on the logit scale. The horizontal green line is at 30% for reference

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Statistical Innovation

Table 2 Dose-Toxicity Curve Scenarios

Scenario	Dose (mg)												
	25	50	80	140	200	300	400	600	800	1000	1200	1400	1600
All Safe	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.03	0.05	0.08	0.12	0.18	0.27
MTD=1000	0.00	0.00	0.00	0.01	0.02	0.03	0.06	0.12	0.20	0.28	0.36	0.43	0.50
MTD=800	0.00	0.00	0.00	0.00	0.01	0.02	0.05	0.13	0.23	0.34	0.45	0.55	0.63
MTD=800 (flatter)	0.00	0.01	0.01	0.03	0.04	0.08	0.12	0.19	0.27	0.34	0.41	0.46	0.51
MTD=600	0.00	0.01	0.02	0.04	0.06	0.11	0.16	0.26	0.35	0.42	0.49	0.55	0.60
MTD=600 (steep)	0.00	0.00	0.01	0.02	0.04	0.09	0.14	0.25	0.36	0.46	0.54	0.61	0.66
MTD=400	0.02	0.05	0.07	0.12	0.17	0.23	0.29	0.38	0.44	0.50	0.55	0.58	0.62
MTD=200	0.02	0.04	0.08	0.17	0.26	0.39	0.50	0.65	0.74	0.80	0.84	0.87	0.89
MTD=80	0.11	0.20	0.29	0.41	0.50	0.60	0.67	0.75	0.80	0.83	0.86	0.88	0.89
All Toxic	0.33	0.36	0.40	0.45	0.50	0.56	0.61	0.68	0.73	0.77	0.79	0.82	0.83

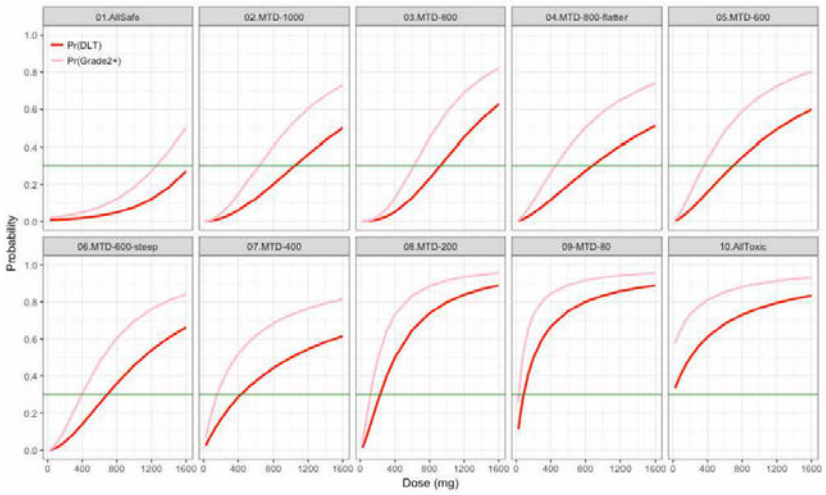

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Figure 1:Dose-Toxicity curve scenarios. The red curve is the probability of DLT and the pink line is the probability of a Grade 2 or higher toxicity.

5.2 Overall Operating Characteristics

For each of the 10 scenarios we have simulated 1000 different trials. For each trial we identify the selected MTD, the number of subjects on each dose, and the average fitted toxicity curve. Note that generally NO phase 1 design is strongly effective in identifying the MTD, given the small sample sizes that are employed in phase 1 trials. In addition, note that toxicity curves are typically poorly estimated for values away from the MTD (estimating the higher end of the toxicity curve would require data from potentially unsafe doses, something the CRM is designed to prevent). The central goal is **only** to estimate the curve well enough to determine where it crosses the threshold of 0.30.

The table below shows the estimated proportion of trials that the proposed CRM selects exactly the correct MTD and the average sample size.

Table 3 Average Behavior

Scenario	Proportion correct MTD selection	Expected sample size
All Safe	0.862	22.4
MTD=1000	0.247	27.7
MTD=800	0.429	26.6
MTD=800 (flatter)	0.279	25.9
MTD=600	0.310	24.3
MTD=600 (steep)	0.356	24.0
MTD=400	0.329	21.9
MTD=200	0.468	20.6
MTD=80	0.430	18.1
All Toxic	NA	12.5

5.3 Dose Selection Probabilities

The following table shows the proportion of times each dose was selected as the MTD. As with any phase 1 design with limited sample sizes, it is very difficult to discern the difference between a 30% and a rate that is slightly higher or lower; thus while the model generally is most likely to pick the MTD in each scenario, there remains a decent chance of selecting a dose one below or above the MTD as well (which would occur if the data just above the MTD randomly had fewer DLTs or many DLTs).

The design is also generally more likely to select one of the main dose levels as opposed to the intermediate doses. This phenomenon occurs because the escalation rules allow the intermediate doses to be skipped, and thus they are only visited once toxicities have been observed.

Table 5 Design: Dose Selection Probabilities

Scenario	Dose (mg)													
	<25	25	50	80	140	200	300	400	600	800	1000	1200	1400	1600
All Safe	0.000	0.000	0.000	0.001	0.000	0.001	0.000	0.001	0.002	0.003	0.009	0.065	0.056	0.862
MTD=1000	0.000	0.000	0.000	0.000	0.000	0.002	0.002	0.040	0.145	0.279	0.247	0.160	0.036	0.089
MTD=800	0.000	0.000	0.000	0.000	0.000	0.001	0.001	0.050	0.223	0.429	0.205	0.065	0.012	0.014
MTD=800 (flatter)	0.000	0.000	0.000	0.001	0.000	0.013	0.015	0.172	0.258	0.279	0.132	0.066	0.019	0.045
MTD=600	0.000	0.000	0.000	0.001	0.000	0.029	0.039	0.348	0.310	0.192	0.048	0.020	0.004	0.009
MTD=600 (steep)	0.000	0.000	0.000	0.001	0.000	0.017	0.028	0.354	0.356	0.195	0.036	0.009	0.000	0.004
MTD=400	0.004	0.003	0.004	0.053	0.056	0.230	0.160	0.329	0.103	0.046	0.008	0.002	0.000	0.002
MTD=200	0.003	0.003	0.007	0.148	0.217	0.468	0.094	0.059	0.000	0.001	0.000	0.000	0.000	0.000
MTD=80	0.082	0.109	0.233	0.430	0.090	0.052	0.001	0.003	0.000	0.000	0.000	0.000	0.000	0.000
All Toxic	0.516	0.220	0.087	0.127	0.024	0.021	0.004	0.001	0.000	0.000	0.000	0.000	0.000	0.000

5.4 Average Sample Size per Dose

The following table shows the average number of subjects per dose for the CRM. For scenarios where the MTD is in the middle or upper end of the dose range, we

observe that the main doses levels typically enroll a single subject, with zero subjects on the intermediate doses.

Table 6 Average Sample Size per Dose

Scenario	Dose (mg)												
	25	50	80	140	200	300	400	600	800	1000	1200	1400	1600
All Safe	1.0	0.0	1.1	0.0	1.2	0.1	1.3	0.4	2.0	1.3	3.2	2.3	8.4
MTD=1000	1.0	0.0	1.0	0.0	1.2	0.3	2.4	3.3	5.6	4.3	4.0	1.9	2.6
MTD=800	1.0	0.0	1.0	0.0	1.2	0.3	2.7	4.4	6.6	4.0	3.2	0.9	1.3
MTD=800 (flatter)	1.0	0.0	1.1	0.1	1.7	0.8	4.0	4.1	5.2	2.9	2.5	1.0	1.5
MTD=600	1.0	0.0	1.2	0.1	2.1	1.5	5.5	4.4	4.3	1.7	1.5	0.4	0.6
MTD=600 (steep)	1.0	0.0	1.1	0.1	1.8	1.3	5.7	4.9	4.4	1.5	1.4	0.3	0.4
MTD=400	1.2	0.2	2.3	1.3	4.3	2.8	5.1	2.0	1.8	0.3	0.5	0.1	0.1
MTD=200	1.2	0.3	3.6	3.4	6.5	2.3	2.7	0.2	0.4	0.0	0.0	0.0	0.0
MTD=80	3.3	3.2	6.3	2.1	2.5	0.2	0.5	0.0	0.1	0.0	0.0	0.0	0.0
All Toxic	5.4	1.9	3.2	0.6	1.0	0.1	0.2	0.0	0.0	0.0	0.0	0.0	0.0

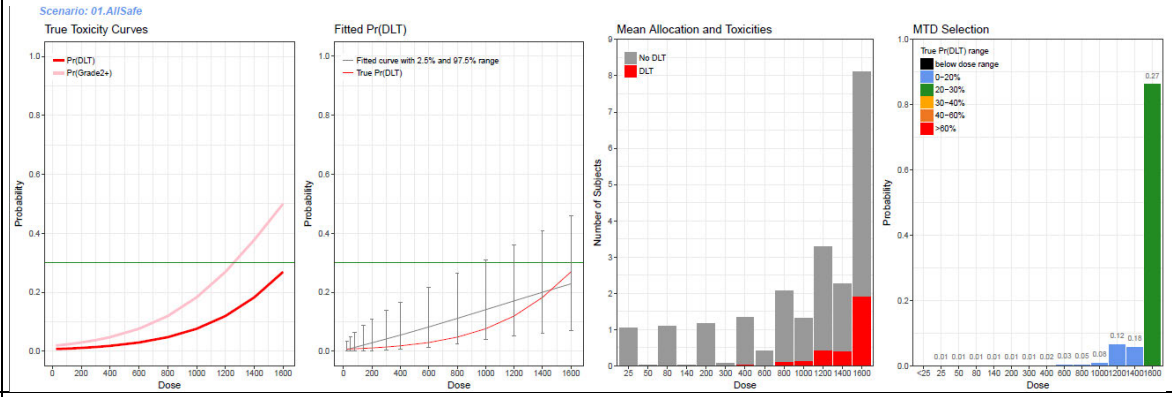
Appendix 3 Additional Performance Details of the mCRM

In this appendix, additional operating characteristics of the mCRM are presented. For each of the 10 scenarios below, the following is presented:

- The assumed dose-probability of DLT relationship (red curve), assumed dose-probability of relevant grade 2 or higher toxicity relationship that triggers a shift from single-subject cohorts to 3 subjects-cohorts (pink curve) and the target toxicity level (green horizontal line).
- Pr(DLT): An illustration of how the final model estimates the true (assumed) dose-dose-probability of DLT relationship. The final model is illustrated by a grey curve with bars denoting a 95% credible range while the true relationship is illustrated by a red curve.
- Allocation and Toxicities: bars denote the expected number of subjects per dose level, of which the red bars denote the expected number of subjects with DLTs per dose level.
- Proportion each Dose selected as MTD: golden brown bars denote the probability that the final mCRM-model will identify a certain dose level as the MTD.

Figure 17-1 Performance of mCRM

b1



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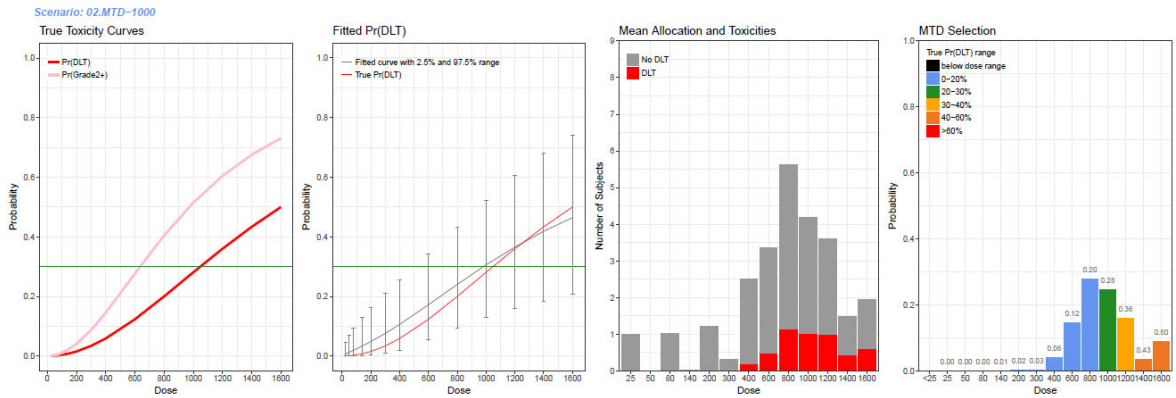

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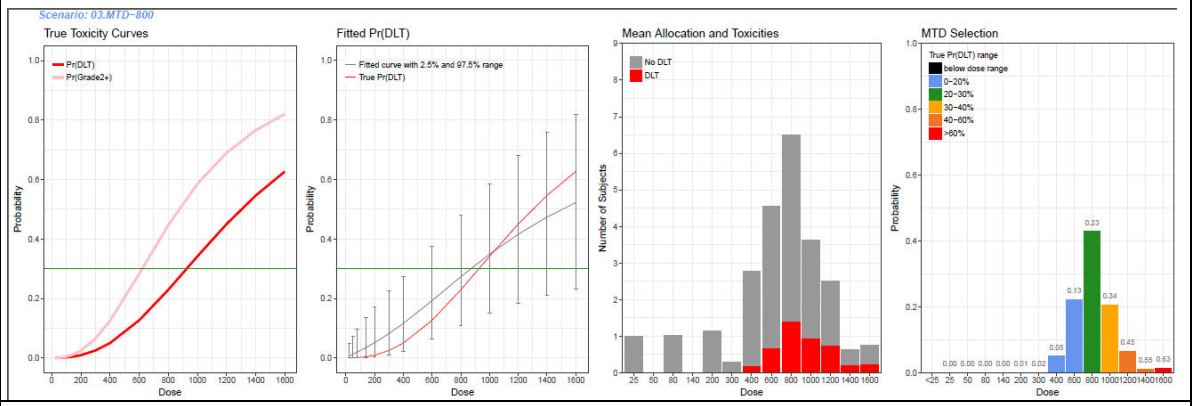
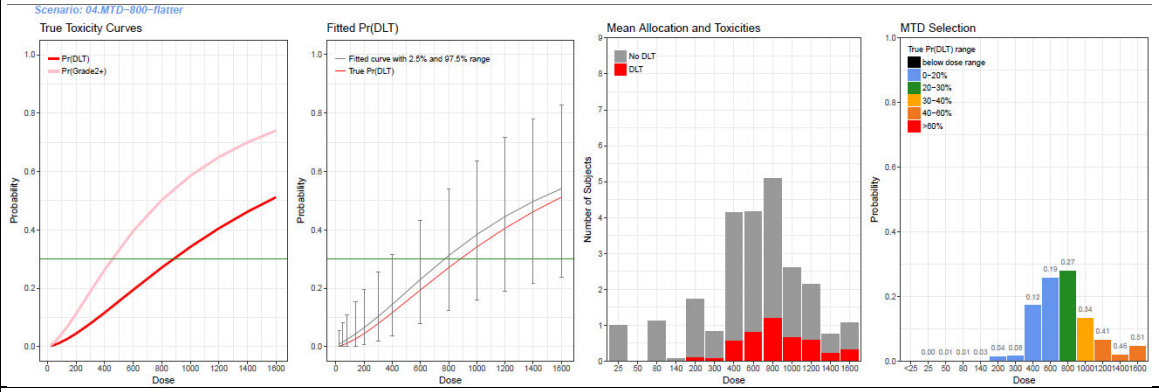

Scenario: 03.MTD−800
True Toxicity Curves
Fitted Pr(DLT)
Mean Allocation and Toxicities
MTD Selection
Probability
Number of Subjects
Dose

b4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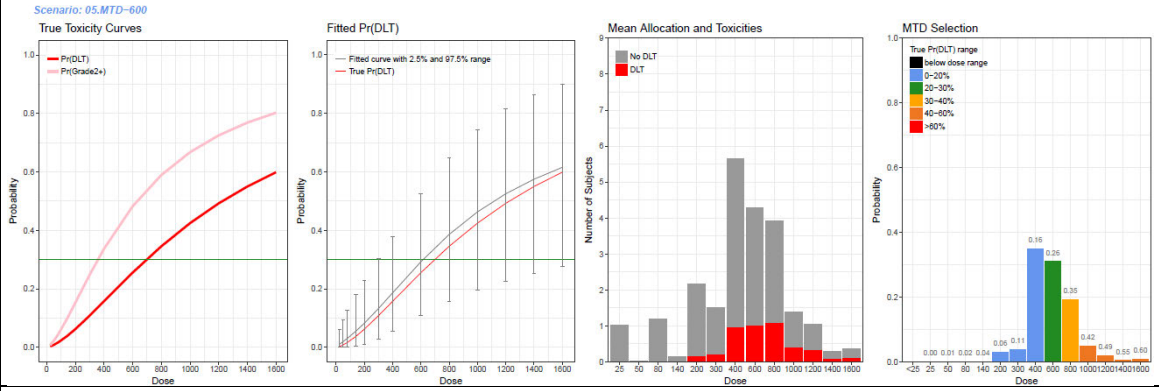
True Toxicity Curves
Fitted Pr(DLT)
Mean Allocation and Toxicities
MTD Selection
Probability
Number of Subjects
Dose

b5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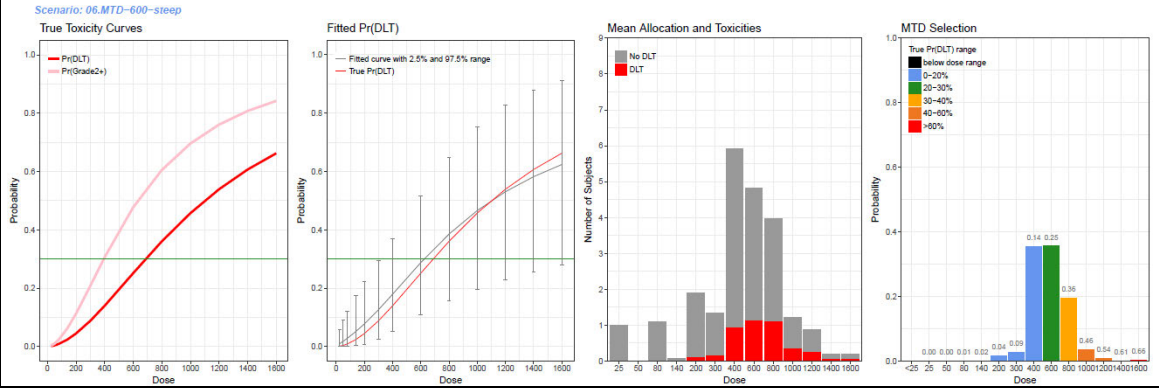
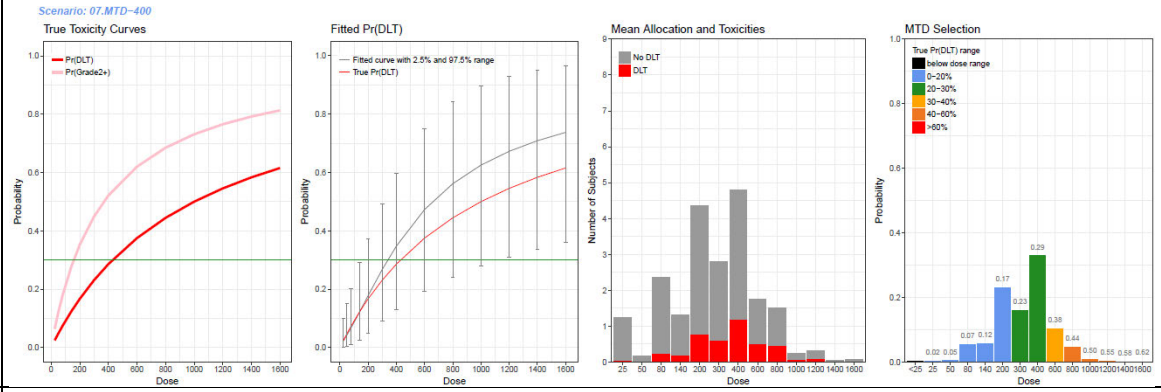
True Toxicity Curves
Fitted Pr(DLT)
Mean Allocation and Toxicities
MTD Selection
Probability
Number of Subjects
Dose

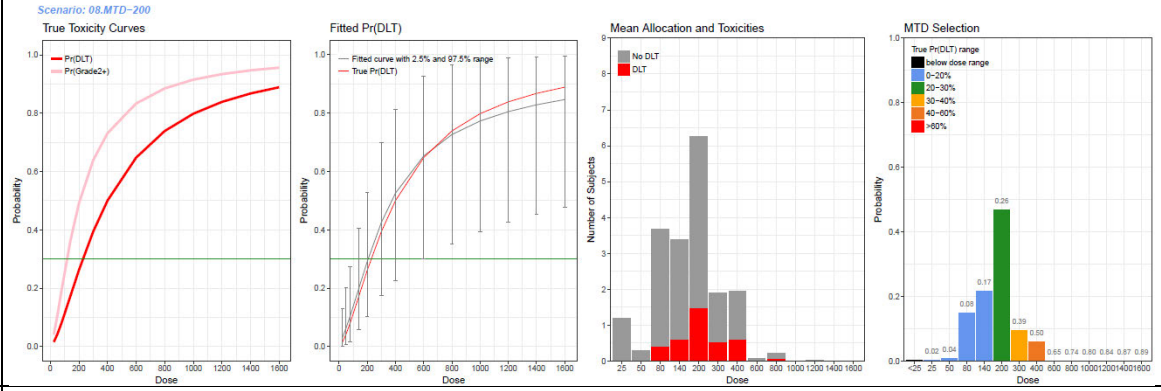
b6


Scenario: 06.MTD−600−steep
True Toxicity Curves
Fitted Pr(DLT)
Mean Allocation and Toxicities
MTD Selection
Probability
Number of Subjects
Dose

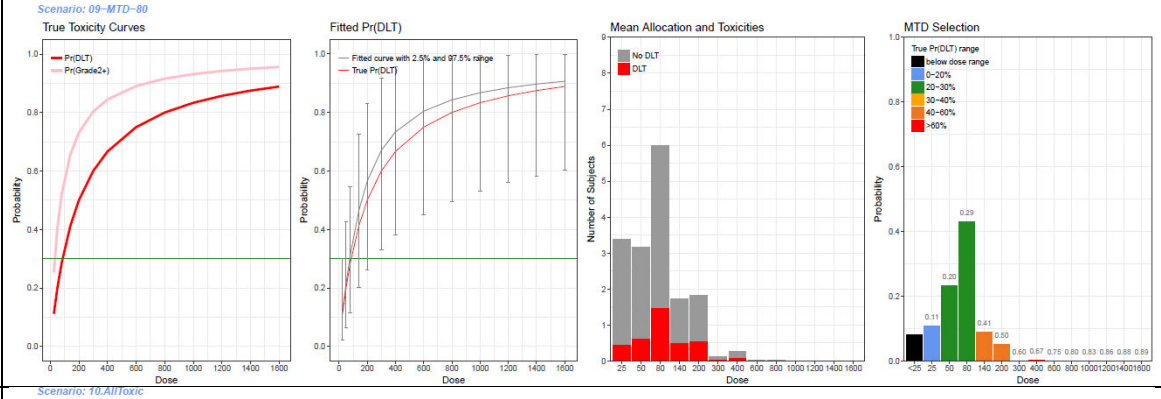
b7


Scenario: 07.MTD~400
True Toxicity Curves
Fitted Pr(DLT)
Mean Allocation and Toxicities
MTD Selection
Probability
Number of Subjects
Dose
Pr(DLT)
Pr(Grade2+)
Fitted curve with 2.5% and 97.5% range
True Pr(DLT)
No DLT
DLT
True Pr(DLT) range
below dose range
0~20%
20~30%
30~40%
40~60%
>60%

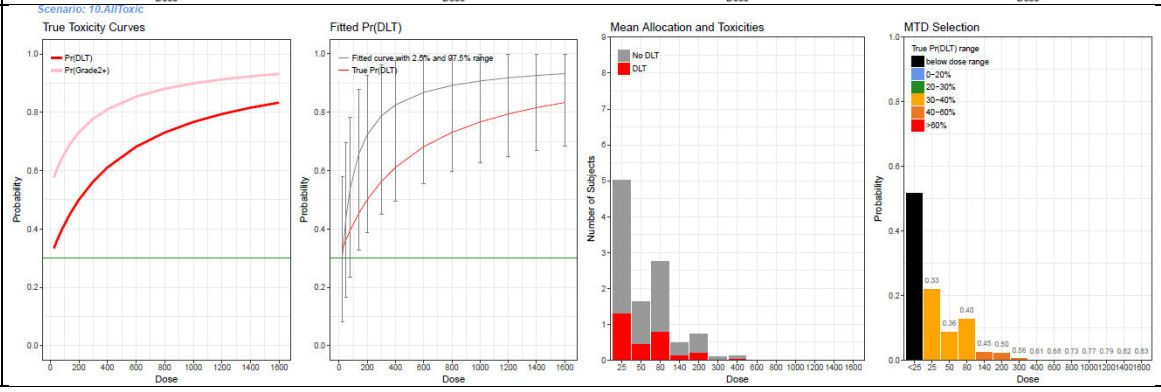
b8


Scenario: 08.MTD~200
True Toxicity Curves
Fitted Pr(DLT)
Mean Allocation and Toxicities
MTD Selection
Probability
Number of Subjects
Dose
Pr(DLT)
Pr(Grade2+)
Fitted curve with 2.5% and 97.5% range
True Pr(DLT)
No DLT
DLT
True Pr(DLT) range
below dose range
0~20%
20~30%
30~40%
40~60%
>60%

b9


Scenario: 09~MTD~80
True Toxicity Curves
Fitted Pr(DLT)
Mean Allocation and Toxicities
MTD Selection
Probability
Number of Subjects
Dose
Pr(DLT)
Pr(Grade2+)
Fitted curve with 2.5% and 97.5% range
True Pr(DLT)
No DLT
DLT
True Pr(DLT) range
below dose range
0~20%
20~30%
30~40%
40~60%
>60%

b10


Scenario: 10.AllToxic
True Toxicity Curves
Fitted Pr(DLT)
Mean Allocation and Toxicities
MTD Selection
Probability
Number of Subjects
Dose
Pr(DLT)
Pr(Grade2+)
Fitted curve with 2.5% and 97.5% range
True Pr(DLT)
No DLT
DLT
True Pr(DLT) range
below dose range
0~20%
20~30%
30~40%
40~60%
>60%

Appendix 4 Country Specifics

Any elements in the protocol that are only applicable to sites in certain regions are clearly marked as such in Table 17-2 and are not applicable to sites in other regions.

Table 17-2 Expansion Cohorts

Cohort No.	Global or Regional
EC1	Global – enrollment completed
EC2	Global – enrollment completed
EC3	Global – enrollment completed
EC4	Global – enrollment completed
EC5	Global – enrollment completed
EC6	Global – enrollment completed
EC7	Global – enrollment completed
EC8	Georgia – enrollment completed
EC9 (Docetaxel Combination)	US and Israel – enrollment completed
EC10	Global – enrollment completed
EC11A (Pembrolizumab Combination)	Global– enrollment completed
EC11B (Pembrolizumab Combination)	Global– enrollment completed
EC12	Global– enrollment completed
EC13	Global– enrollment completed

EC=expansion cohort.

Table 17-3 IMP EU Authorisation Status

IMP Drug Name	EU Authorisation Status
GEN1046	Unauthorised
Pembrolizumab	Authorised
Docetaxel	Authorised
Cisplatin	Authorised
Pemetrexed	Authorised
Carboplatin	Authorised
Paclitaxel	Authorised
Nab-paclitaxel	Authorised

18 INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure that they are fully informed regarding the trial drug, the conduct of the trial, and the obligations of confidentiality.

NOTE: The Coordinating Investigator section below is applicable only to the country-specific coordinating investigators within the EU.

Coordinating Investigator (where required):

Name (typed or printed):

Institution and Address: _____

_____

_____

_____

_____

Signature: _____ Date: _____
(DD-Mmm-YYYY)

Principal (Site) Investigator:

Name (typed or printed):

Institution and Address: _____

_____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(DD-Mmm-YYYY)

Note: If the address or telephone number of the investigator changes during the course of the trial, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.