

CLINICAL TRIAL PROTOCOL

Protocol Title	First-In-Human, Open-Label, Dose Escalation Trial with Expansion Cohorts to Evaluate the Safety and Preliminary Efficacy of GEN1055 as Monotherapy and as Combination Therapy in Subjects with Malignant Solid Tumors.	
Protocol Number	GCT1055-01	
Compound	GEN1055	
Brief Title	Trial to assess the safety and preliminary efficacy of GEN1055 on malignant solid tumors as monotherapy and as combination therapy.	
Trial Phase	1/2a	
Sponsor Name	Genmab*	
Collaborator Name	BioNTech	
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** This protocol was approved via electronic signature on the approval page appended to the document.

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The sponsor contact information page will be provided separately; listing the trial responsible medical officer, as well as the CRO(s), laboratory(ies) (names and addresses), and other technical/medical services used.

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 agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), the principles in the Declaration of Helsinki, the Japanese Ministerial Ordinance on GCP, and applicable national or regional regulations/guidelines.

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 treatment, the conduct of the trial, and the obligations of confidentiality.

Principal (Site) Investigator:	
Name (typed or printed):	
Institution and Address:	
Telephone Number:	

Signature: _____ Date: _____
(DD-Mmm-YYYY)

NOTE: The Coordinating Investigator section below is applicable only to the country-specific coordinating investigators within the European Union, where applicable.

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(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.

Completed and signed forms will be filed separately from the protocol.

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List of Abbreviations and Definitions

Abbreviation	Definition
%CV	percentage coefficient of variation
1L	first-line
2L	second-line
2L+	second and later treatment lines
5-FU	fluorouracil
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
AMP	auxiliary medicinal product
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
AUC _{0-inf}	area under the concentration-time curve from time 0 to infinity
AUC _{0-tlast}	area under the concentration-time curve from time 0 to last quantifiable sample
Baseline	the last available measurement prior to first dosing, if not otherwise specified
BLI	biolayer interferometry
BOIN	Bayesian optimal interval
BOR	best overall response
BRCA	breast cancer
C	cycle
CBC	complete blood count
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
cfDNA	cell-free deoxyribonucleic acid
CE	Conformité Européenne
CFR	Code of Federal Regulations
CL	clearance
C _{max}	maximum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019

Abbreviation	Definition
CPI	checkpoint inhibitor
CPS	Combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CT	computed tomography
CCI	CCI
CTIS	Clinical Trials Information System
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C _{trough}	predose trough concentration
D	day
DCR	disease control rate
DDS	dose-determining analysis set
DEC	Dose Escalation Committee
DL	dose level
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DoR	duration of response
EC	expansion cohort
EC ₅₀	half maximal effective concentration
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
End of trial	the date of the last visit/trial contact of the last subject in the trial globally
EoT	end of treatment
ER	estrogen receptor
EU	European Union
exoRNA	exosomal RNA
FAS	full analysis set
Fc	crystallizable fragment
FcγR	Fc gamma receptor
FDA	Food and Drug Administration

Abbreviation	Definition
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
CCI	CCI
CCI	CCI
HNSTD	highest non-severely toxic dose
HPV	human papillomavirus
IB	Investigator's Brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDCR	immune disease control rate
iDoR	immune duration of response
IEC	Independent Ethics Committee
IFN γ	interferon gamma
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
iORR	immune objective response rate
iPFS	immune progression-free survival
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune Response Evaluation Criteria in Solid Tumours

Abbreviation	Definition
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous(ly)
K _D	dissociation constant
KIRC	clear cell renal cell carcinoma
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LUAD	lung adenocarcinoma
LUSC	lung squamous cell carcinoma
mAb	monoclonal antibody
MABEL	minimum anticipated biological effect level
MAD	maximum administered dose
mBOIN	modified Bayesian optimal interval
MoA	mechanism of action
mOS	median overall survival
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI	microsatellite instability
MTD	maximum tolerated dose
N/A	not applicable
NASH	nonalcoholic steatohepatitis
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NK	natural killer
NOAEL	no-observed-adverse-effect level
CCI	CCI
NSQ	non-squamous
ORR	objective response rate
OS	overall survival
PAAD	pancreatic adenocarcinoma
PAD	pharmacologically active dose
PARP	poly(ADP-ribose) polymerase
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic
PD	progressive disease
PD-1	programmed cell death protein 1

Abbreviation	Definition
PDAC	pancreatic ductal adenocarcinoma
PD-L1	programmed cell death ligand 1
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic(s)
PPoS	predictive probability of success
PR	partial response
Primary completion date	the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the trial concluded as planned in the protocol or was terminated early
PRO	patient-reported outcome
PS	performance status
PSA	prostate-specific antigen
Q3W	every 3 weeks
QA	quality assurance
QTc	corrected QT interval
RBC	red blood cell
RCC	renal cell carcinoma
RANK-L	Receptor activator of nuclear factor-(kappa)B ligand
RECIST	Response Evaluation Criteria in Solid Tumours
RET	ret proto-oncogene
RO	receptor occupancy
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCID	severe combined immunodeficient
SCr	serum creatinine
SD	stable disease
SFU	safety follow-up visit
SmPC	summary of product characteristics
SoC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
t _{1/2}	half-life
TCGA	The Cancer Genome Atlas
CCI	CCI

Abbreviation	Definition
TEAE	treatment-emergent adverse event
$t_{\max}$	time to reach $C_{\max}$
CCI	CCI
TNF	tumor necrosis factor
TNFRSF	Tumor Necrosis Factor Receptor Super Family
TNM	tumor nodes metastasis
Trial drug(s)	specifically refers to IMP(s)
Trial treatment	any IMP, AMP, or medical device(s) intended to be administered to a trial subject according to the trial protocol
TTR	time to response
ULN	upper limit of normal
US	United States
USA	United States of America
USPI	United States prescribing information

1 PROTOCOL SUMMARY

1.1 Trial Synopsis

Protocol Title:	First-In-Human, Open-Label, Dose Escalation Trial with Expansion Cohorts to Evaluate the Safety and Preliminary Efficacy of GEN1055 as Monotherapy and as Combination Therapy in Subjects with Malignant Solid Tumors.		
Brief Title:	Trial to assess the safety and preliminary efficacy of GEN1055 on malignant solid tumors as monotherapy and as combination therapy.		
Phase:	1/2a		
Indication:	Solid tumors, CCI [REDACTED]		
Rationale: GEN1055 (BNT315, HexaBody-OX40; jointly developed by Genmab and BioNTech) is a hexamerization-enhanced, Fc-silenced immunoglobulin G1 antibody targeting OX40. Upon binding to cell surface-expressed OX40, it promotes OX40 receptor clustering on the cell surface, which results in Fc gamma receptor-independent agonistic signaling. OX40 agonists have demonstrated preliminary clinical activity and were well tolerated as monotherapy, making them attractive combination partners. The purpose of this phase 1/2a trial is to characterize the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic profiles, and assess preliminary antitumor activity of GEN1055 as both monotherapy and as combination therapy in subjects with malignant, non-central nervous system (non-CNS), primary solid tumors who have metastatic or advanced disease. Provided that the safety profile of GEN1055 monotherapy is acceptable, the safety and efficacy of GEN1055 in combination with programmed cell death protein 1 (PD-1)-blocking antibody pembrolizumab will also be explored. A subsequent expansion part will further evaluate safety and serve to establish a preliminary assessment of efficacy of both monotherapy and as combination therapy in selected indications.			
Objectives and Endpoints (Escalation):			
Objectives		Endpoints	
Primary			
Evaluate the safety of GEN1055 as monotherapy and as combination therapy with pembrolizumab		Incidence and severity of adverse events (AEs)	
Determine expansion doses of GEN1055 as monotherapy and as combination therapy with pembrolizumab		Incidence of dose-limiting toxicities (DLTs)	
Secondary			
Characterize the PK properties of GEN1055 as monotherapy and as combination therapy with pembrolizumab		PK parameters for GEN1055: - Maximum concentration (C_{max}) - Time to reach C_{max} (t_{max}) - Predose trough concentration (C_{trough}) - Area under the concentration-time curve from time 0 to last quantifiable sample (AUC_{0-last}) - Area under the concentration-time curve from time 0 to infinity (AUC_{0-inf}) - Half-life ($t_{1/2}$) - Clearance (CL)	
Evaluate immunogenicity of GEN1055		Anti-drug antibody (ADA) response to GEN1055 as monotherapy and as combination therapy with pembrolizumab	
Assess the antitumor activity of GEN1055 as monotherapy and as combination therapy with pembrolizumab		According to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 as assessed by investigator: - Objective response rate (ORR) - Duration of response (DoR)	

	- Time to response (TTR) - Disease control rate (DCR)
Objectives and Endpoints (Expansion):	
Objectives	Endpoints
Primary	
Assess the antitumor activity of GEN1055 as monotherapy and as combination therapy	According to RECIST v1.1 as assessed by investigator: ORR
Secondary	
Assess the antitumor activity of GEN1055 as monotherapy and as combination therapy	According to RECIST v1.1 as assessed by investigator: - DoR - TTR - DCR
Assess the antitumor efficacy of GEN1055 as monotherapy and as combination therapy	- Progression-free survival (PFS) according to RECIST v1.1 as assessed by investigator - Overall survival (OS)
Evaluate safety of GEN1055 as monotherapy and as combination therapy	Incidence and severity of AEs
Evaluate immunogenicity of GEN1055 as monotherapy and as combination therapy	ADA response to GEN1055 as monotherapy and as combination therapy
Characterize the PK of GEN1055 as monotherapy and in combination therapy	PK parameters for GEN1055: - C_{max} - t_{max} - C_{trough} - AUC_{0-1ast} - AUC_{0-inf} - t_½ - CL
Trial Design and Duration: This is a phase 1/2a open-label, multicenter, multinational trial in subjects with malignant, primary solid tumors who have metastatic or advanced disease to evaluate the safety, tolerability, PK and pharmacodynamic profiles, and assess preliminary antitumor activity of trial treatment. The trial consists of escalation (phase 1a/1b) and expansion (phase 2a) parts as follows: - Phase 1a: dose escalation with GEN1055 as monotherapy (approximately 50 subjects) - Phase 1b: dose escalation with GEN1055 in combination with a fixed dose of pembrolizumab (GEN1055+pembrolizumab) (approximately 40 subjects) - Phase 2a: expansion - Expansion cohort (EC)1: CCI [REDACTED], GEN1055 (approximately 20 subjects) - EC2: CCI [REDACTED], GEN1055+pembrolizumab (approximately 40 subjects) - EC3: CCI [REDACTED], GEN1055+pembrolizumab+chemotherapy (pemetrexed+cisplatin or carboplatin) (up to 40 subjects) - EC4: CCI [REDACTED], GEN1055+pembrolizumab+chemotherapy (carboplatin+paclitaxel or nab-paclitaxel) (up to 40 subjects) - EC5: CCI [REDACTED], GEN1055+pembrolizumab+chemotherapy (paclitaxel or nab-paclitaxel or gemcitabine+carboplatin) (approximately 40 subjects) Each part will consist of: - Screening (up to 21 days prior to Cycle 1 Day 1 [C1D1]) - An estimated 24-month treatment period (from C1D1 until discontinuation of trial treatment) - A first safety follow-up visit 30 days after the last dose of trial treatment - A second safety follow-up visit 90 days after the last dose of trial treatment - Survival follow-up starting after the last safety follow-up visit	

For pembrolizumab-containing regimens treatment should not exceed 24 months.

Number of Subjects:

Approximately 270 subjects will be enrolled in this trial.

Summary of Key Eligibility Criteria:

Key Inclusion Criteria:

All cohorts:

- Be at least 18 (or the legal age of consent in the jurisdiction in which the trial is taking place) years of age.
- Have measurable disease according to RECIST v1.1.
- Provide all pre-baseline scans since failure of last prior therapy (ie, documented radiographic progressive disease [PD]), if available.
- Have Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 to 1 at screening and on C1D1 pretreatment. *Note: Do not perform C1D1 ECOG PS if within 3 days of Screening ECOG PS.*
- Provide a biopsy (ie, formalin-fixed paraffin-embedded slides/block). A fresh biopsy taken during the screening period is preferred, unless medically unfeasible and after review and approval by the sponsor. If this cannot be provided, a biopsy taken after failure/stop of last prior treatment and taken within 6 months prior to C1D1 may be provided.
Note: Documentation of biopsy collection and shipment must be submitted to the sponsor as a part of the eligibility package prior to administration of the first dose of trial treatment.

Phase 1a and 1b:

- Have histologically or cytologically confirmed non-CNS primary solid tumors who have metastatic or advanced disease.
- Have progressed on standard of care (SoC) therapy which should include platinum-based chemotherapy and anti-PD-1/PD-L1 therapies, if applicable for the tumor type, or for whom there is no available standard therapy likely to provide clinical benefit, and for whom experimental therapy with GEN1055 or GEN1055+pembrolizumab may be beneficial, in the opinion of the investigator.

Phase 2a – Expansion:

- Have histologically or cytologically confirmed diagnosis of 1 of the following:
 - CCI [REDACTED]
 - CCI [REDACTED]
 - CCI [REDACTED]

EC1

- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]

- CCI [REDACTED]

EC2:

- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]

EC3:

- CCI [REDACTED]
 - CCI [REDACTED]
 - CCI [REDACTED]

EC4:

- CCI [REDACTED]
 - CCI [REDACTED]
 - CCI [REDACTED]

EC5:

- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]

Key Exclusion Criteria:

- Has uncontrolled intercurrent illness, including but not limited to:

- Ongoing or active infection requiring intravenous (IV) treatment with anti-infective therapy administered less than 2 weeks prior to first dose (including coronavirus disease 2019 [COVID-19] infection). *Note: a past COVID-19 infection may be a risk factor, but if resolved and the subject is vaccinated, it may be allowable to enroll the subject).*
- Significant cardiovascular impairment including:
 - Symptomatic congestive heart failure (Class 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 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg, despite optimal medical management.
 - Prolonged corrected QT interval at baseline of ≥ 470 milliseconds using Fridericia's QT correction formula.
- Ongoing or recent (within 1 year of screening) 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 condition is not exclusionary: Residual hypothyroidism that requires only hormone replacement.
- History of grade 3 or higher irAEs that led to treatment discontinuation of a checkpoint inhibitor (CPI). A subject with irAEs below grade 3 that led to discontinuation should be discussed with the sponsor. Grade 3 irAEs that have fully recovered may also be discussed.
- History of chronic liver disease (eg, alcoholic hepatitis or nonalcoholic steatohepatitis), drug-related or autoimmune hepatitis, or evidence of hepatic cirrhosis.
- Evidence of interstitial lung disease.
- Ongoing pneumonitis (any grade) including any radiological change of ongoing pneumonitis at baseline or history of noninfectious drug-, immune-, or radiation-related pneumonitis that has required steroids.
- Has been exposed to any of the following prior therapies/treatments within the specified timeframes:
 - Treatment with an anticancer agent within 4 weeks or for systemic therapies within 5 half-lives of the drug, whichever is shorter, prior to trial treatment administration.
 - Condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first treatment. Inhaled or topical steroids, and adrenal or pituitary replacement steroid >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
 - Has received granulocyte or granulocyte/macrophage colony-stimulating factor support within 2 weeks prior to first trial treatment administration or is chronically transfusion-dependent.
 - RT within 14 days before the planned first dose of trial treatment. Palliative RT of bone metastases up to 7 days prior to C1D1 will be allowed.
 - **Only for EC1:** Discontinued treatment due to PD within the first 12 weeks of a CPI-containing treatment.
- Hepatitis (testing for hepatitis B or C is not required unless mandated by local health authority):
 - Hepatitis B virus (HBV): Has a medical history or positive serology for HBV (defined as positive for hepatitis B surface antigen or HBV DNA).
 - Above is not exclusionary if deemed due to vaccination, resolved natural infection, or passive immunization due to immunoglobulin therapy.
 - Hepatitis C virus (HCV): Known active HCV infection (defined as positive for HCV RNA [qualitative]).

Trial Treatment:

Dose escalation:

- GEN1055 will be administered IV every 3 weeks (Q3W) at increasing doses from **CCI** as monotherapy and at approximately 3 dose levels in combination with a fixed dose of pembrolizumab.
- Pembrolizumab at 200 mg will be administered IV Q3W.

Expansion:

- GEN1055 will be administered IV Q3W at a dose level selected from the dose escalation part.

- Pembrolizumab will be administered IV at 200 mg Q3W.

Other Trial Treatment:

- Pemetrexed will be administered IV at 500 mg/m² Q3W
- Paclitaxel will be administered IV at 200 mg/m² Q3W for 4 cycles **or** at 90 mg/m² on Days 1, 8 and 15 of an every 4 week (Q4W) cycle
- Nab-paclitaxel will be administered IV at 100 mg/m² on Day 1, 8 and 15 of a Q3W cycle for 4 cycles **or** 100 mg/m² on Days 1, 8 and 15 of a Q4W cycle
- Gemcitabine will be administered IV at 1000 mg/m² with Carboplatin AUC 2 mg/mL/min on Days 1 and 8 of a Q3W cycle
- Cisplatin will be administered IV at 75 mg/m² Q3W for 4 cycles
- Carboplatin will be administered IV at AUC 5 or AUC 6 Q3W for 4 cycles

Statistics:

There is no formal hypothesis to be tested in the dose escalation nor in the expansion part.

In the dose escalation part, the choice of an optimal monotherapy and combination dose will be guided by Bayesian optimal interval method, with a flat dose level of pembrolizumab.

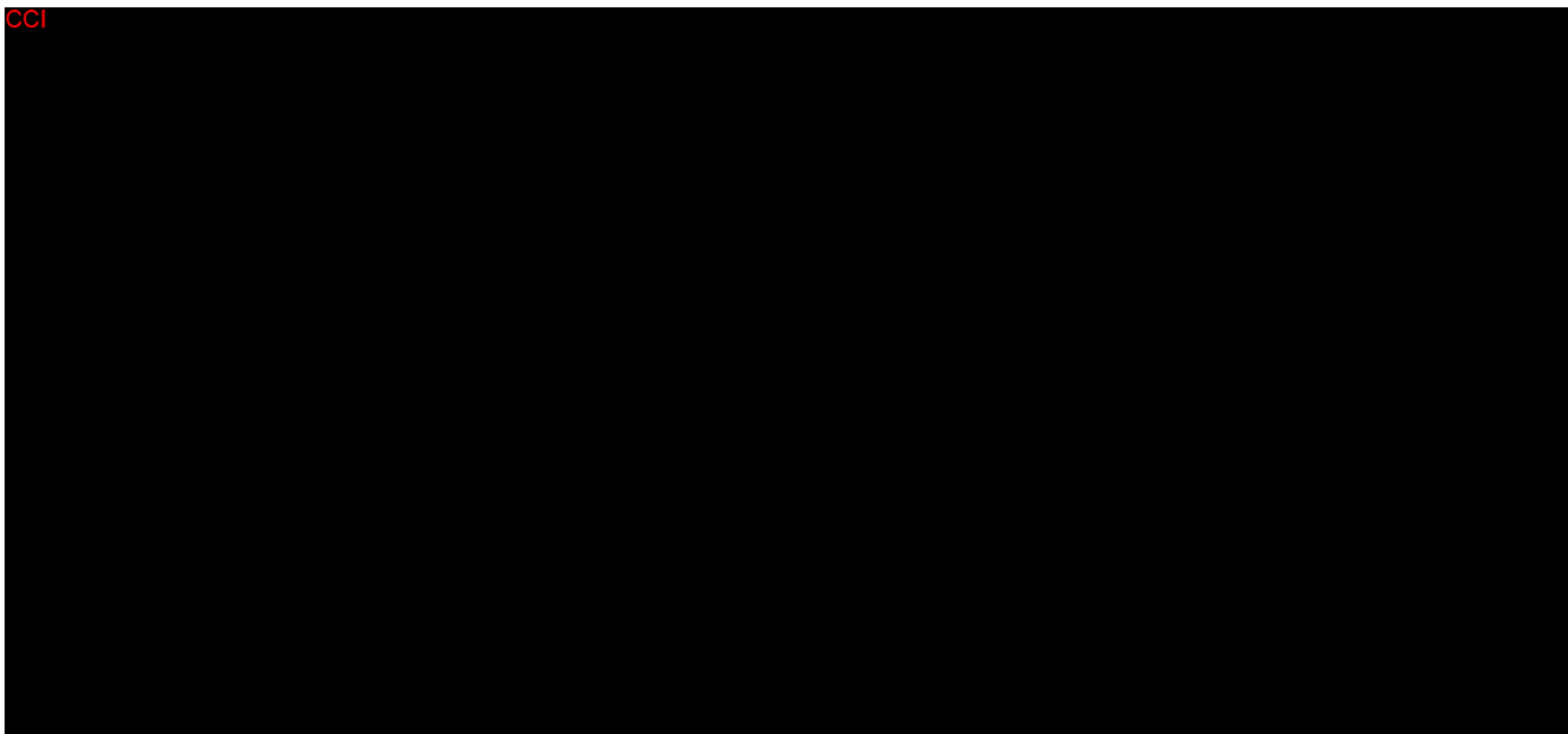
The expansion part will collect data to establish proof-of-activity in a stagewise manner. The primary endpoint for the expansion part of the trial is the confirmed ORR as assessed by investigator and classified as per RECIST v1.1. The ORR is defined as the proportion of subjects with best overall response (BOR) of complete response or partial response.

BOR will be summarized in conjunction with the ORR. The estimated ORR and the exact 2-sided 95% confidence interval using the Clopper-Pearson method will be presented. The DCR is defined as the proportion of subjects with BOR of complete response, partial response, or stable disease. The estimated DCR and the exact 2-sided 95% confidence interval using the Clopper-Pearson method will be presented. PFS and OS will be defined for all subjects and presented graphically as well as summarized using survival analysis methods in terms of Kaplan-Meier estimates. DoR and TTR will be presented similar to PFS. Other secondary endpoints will be summarized descriptively.

As up to 80 subjects with CCI could potentially be enrolled, efficacy monitoring has been applied for each of EC3 and EC4. The 2 CCI cohorts will be separately evaluated for efficacy using the predictive probability of success method when data from the first 20 subjects are available in the given cohort. Further characteristics of this approach are dependent on the number of dose regimens selected for the ECs based on results of phase 1a and 1b.

1.2 Schema

Figure 1 Trial Schema



a. In case of PD on GEN1055 monotherapy, subjects may have the option to receive combination therapy with GEN1055+pembrolizumab by following EC2 activities. 1L=first-line; 2L+=second and later treatment lines; BOIN=Bayesian optimal interval; Combi=combination therapy; CPI=checkpoint inhibitor; CPS=combined positive score; DL=dose level; EC=expansion cohort (numbered); CCI [redacted]; MABEL=minimum anticipated biological effect level; MoA=mechanism of action; Mono=monotherapy; N=number of subjects; CCI [redacted]; PD=progressive disease; PD-1=programmed cell death protein 1; PD-L1=programmed cell death ligand 1; pembro; pembrolizumab; Q3W=once every 3 weeks; SoC=standard of care; CCI [redacted]; CCI [redacted]; Tx=treatment.

1.3 Schedule of Activities

Dose Escalation	
Table 1-1	Dose Escalation: Schedule of Activities
Table 1-2	Dose Escalation: Schedule of ECG, Vital Signs, Pharmacokinetics, Immunogenicity
Table 1-3	Dose Escalation: Schedule for Biomarker Assessment
Dose Expansion	
Table 1-4	Expansion: Schedule of Activities
Table 1-5	EC5 Trial Treatment Administrations
Table 1-6	Expansion: Schedule of ECG, Vital Signs, Pharmacokinetics, Immunogenicity
Table 1-7	Expansion: Schedule for Biomarker Assessment

1.3.1 Dose Escalation

Table 1-1 Dose Escalation: Schedule of Activities

Trial Period	SCR ^a	Treatment Period ^b								Post-Treatment				UNS ^c	Section	Notes
Cycle/Visit		C1-C2				C3-C4			C5+	EoT ^d	SFU1 ^e	SFU2 ^f	SvFU ^g			
Cycle Day		D1	D3	D8	D15	D1	D8	D15	D1							
Visit Window (days)		+3 ^h	±1	±1	±1	±3	±1	±1	±3							
General and Safety Assessments																
Informed consent	X														10.1.6	Must be obtained prior to the screening period
Demographics	X														8.1.1	
Diagnosis and disease status	X														8.1.2	
Medical history	X														8.1.3	
Eligibility criteria	X														5	
ECOG PS	X	X								X	X			X	8.3.5	
Prior anticancer therapy	X														6.7.1	
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X		X	6.7	
Full physical exam	X	X				X			X	X	X			X	8.3.1	
Brief physical exam				X	X		X	X								Performed as indicated by the subject's symptoms, adverse events, or other findings as determined by the investigator.
Vital signs	X	X		X	X	X	X*	X*	X	X	X	X		X	8.3.3	X* For C3 through C4, the D8 and D15 assessments should only be performed as indicated by the subject's symptoms, adverse events, or other findings as determined by the investigator.
AEs	X*	X	X	X	X	X	X	X	X	X	X	X	X [#]	X	8.4	X*: AEs related to protocol-mandated procedures X [#] : No monitoring required, but if investigator becomes aware of a treatment-related SAE, it must be reported.
Height	X														8.3.2	
Weight	X					X			X	X	X	X				
12-lead ECG	X	See Table 1-2													8.3.4	
Prebaseline imaging scans	X															

Table 1-1 Dose Escalation: Schedule of Activities

Trial Period	SCR ^a	Treatment Period ^b								Post-Treatment				UNS ^c	Section	Notes
Cycle/Visit		C1-C2				C3-C4			C5+	EoT ^d	SFU1 ^e	SFU2 ^f	SvFU ^g			
Cycle Day		D1	D3	D8	D15	D1	D8	D15	D1							
Visit Window (days)		+3 ^h	±1	±1	±1	±3	±1	±1	±3							
Prebaseline labs	X														8.3.6	
Subsequent anticancer therapy										X	X	X	X			
Subject disposition	X									X					Will also be recorded at end of trial.	
Survival status													X		7.1.3	
Local Laboratory Assessments (see Table 8-1 for specific analytes)																
Hepatitis/viral serology	X ^{*,#}														8.3.6	*Includes HBV, HCV, HTLV-1, HIV. Only performed if required by local regulations. X [#] All local laboratory samples at the screening visit must be obtained within 7 days prior to C1D1 (with the exception of hepatitis B and C sample, which may be obtained earlier). Screening samples can replace C1D1 if taken within 3 days prior to C1D1. X [*] : Serum pregnancy test required at screening. Additionally, a urine or serum test should be performed within 24 hours of dosing at the start of each subsequent cycle. If a urine pregnancy test is positive, a serum pregnancy test is required to confirm. X [†] Local laboratory samples should be obtained within 3 days before trial treatment administration on Day 1 of each cycle. Laboratory values should be reviewed before dosing.
Endocrine/Thyroid function	X [#]									X				X		
Pregnancy test (serum/urine)	X ^{*,#}	X [*]				X [*]			X [*]	X	X	X		X		
Hematology	X [#]	X [†]	X	X	X	X [†]	X	X	X [†]	X	X	X		X		
Biochemistry	X [#]	X [†]	X	X	X	X [†]	X	X	X [†]	X	X	X		X		
Urinalysis	X [#]	X [†]				X [†]			X [†]	X				X		
Central Laboratory Assessments																
Tumor biopsy	See Table 1-3														8.6.2	
GEN1055 PK	See Table 1-2														8.5	
GEN1055 ADA	See Table 1-2														8.7	
Biomarkers	See Table 1-3														8.6	

Table 1-1 Dose Escalation: Schedule of Activities

Trial Period	SCR ^a	Treatment Period ^b							Post-Treatment				UNS ^c	Section	Notes	
Cycle/Visit		C1-C2				C3-C4			C5+	EoT ^d	SFU1 ^e	SFU2 ^f				SvFU ^g
Cycle Day		D1	D3	D8	D15	D1	D8	D15	D1							
Visit Window (days)		+3 ^h	±1	±1	±1	±3	±1	±1	±3							
Disease-Specific Assessments																
Imaging/disease assessments	X	See Section 8.2														
Trial Treatment Administration																
GEN1055		X				X			X						6	
Pembrolizumab		X				X			X							Only for combination therapy cohorts.

ADA=anti-drug antibody; AE=adverse event; C=cycle; D=day(s); ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; EoT=end of treatment; HBV=hepatitis B virus; HCV=hepatitis C virus; HTLV-1=human T-lymphotropic virus type 1; PK=pharmacokinetic(s); SAE=serious adverse event; SCR=screening; SFU=safety follow-up; SvFU=survival follow-up; UNS=unscheduled.

- The screening period must be completed within 21 days of signing informed consent.
- During the treatment period, all assessments are to be performed prior to trial treatment administration unless otherwise indicated.
- Unscheduled visits may be performed at any time per investigator's discretion. Assessments should be performed as clinically indicated.
- The EoT assessments should be performed as soon as possible after discontinuation of trial treatment and before the start of subsequent therapy.
- The SFU1 visit should be performed 30 (±7) days after last dose of trial treatment or before the start of subsequent therapy, whichever comes first.
- The SFU2 visit should be performed 90 (±7) days after last dose of trial treatment or before the start of subsequent therapy, whichever comes first.
- Survival status will be assessed every 12 weeks (±14 days), beginning from the day the subject receives the last trial treatment administration and continuing until the subject dies, withdraws consent, the subject is lost to follow-up or the trial ends (see Section 7.1.3 for further details). The SvFU can take place at the same time as the SFU2.
- Visit window (+3d) applies to C2D1 only.

Table 1-2 Dose Escalation: Schedule of ECG, Vital Signs, Pharmacokinetics, Immunogenicity

Cycle/Visit	SCR ^a	C1-C2							C3-C4					C5+			EoT	SFU1	SFU2	UNS
Cycle Day		D1				D3	D8	D15	D1			D8	D15	D1						
Hours after dose ^b		Pre	EoI	2h	6h	48h	168h	336h	Pre	EoI	2h	168h	336h	Pre	EoI	2h				
Assessment window			+15m	±30m	±1h	±1d	±1d	±1d		+15m	±30m	±1d	±1d		+15m	±30m				
ECG ^c	X	X ^d	X	X					X	X ^e				X	X ^e		X	X	X	X ^e
Vital signs	X	X ^d	X	X			X	X	X		X	X ^f	X ^f	X		X	X	X	X	X ^e
GEN1055 PK		X	X	X	X	X	X	X	X	X	X ^g	X ^g	X ^g	X	X ^h		X	X	X	X ^e
GEN1055 ADA		X					X ⁱ		X					X ^j			X			

ADA=anti-drug antibody; C=cycle; D/d=day(s); ECG=electrocardiogram; EoI=end of infusion; EoT=end of treatment; h=hour(s); m=minutes; PK=pharmacokinetic(s); Pre=predose; SCR=screening; SFU=safety follow-up; UNS=unscheduled.

- The screening period must be completed within 21 days of signing informed consent.
- For combination therapy, sampling time points relate to the GEN1055 infusion.
- ECGs are to be taken as triplicate assessments up to C8. ECGs are to be submitted for central analysis.
- For combination therapy, both before GEN1055 and before pembrolizumab administrations.
- Optional. For ECGs: as clinically indicated.
- For C3 through C4, the D8 and D15 assessments should only be performed as indicated by the subject's symptoms, adverse events, or other findings as determined by the investigator.
- C3 only.
- Up to C12.
- C1 only.
- Up to C12 at even-numbered cycles only

Table 1-3 Dose Escalation: Schedule for Biomarker Assessment

Cycle/Visit	SCR ^a	C1-C2						C3			C4+	EoT	UNS
Cycle Day		D1			D3	D8	D15	D1	D8	D15	D1		
Hours after dose ^b		Pre	EoI	6h	48h			Pre			Pre		
Assessment window			+15m	±1h	±1d								
Tumor Biopsy	X ^c						X ^d						X ^e
Soluble Factors (eg, cytokines)		X		X	X	X							X ^e
Immunophenotyping (Whole Blood, PBMCs); CCI		X			X	X	X	X	X	X	X ^f	X	X ^e
Receptor Occupancy		X	X ^g		X ^g	X ^g	X ^g						
CCI		X						X			X ^f	X	X ^e
Whole blood for DNA control	X												

C=cycle; CCI; D/d=day(s); EoI=end of infusion; EoT=end of treatment; h=hour(s); m=minutes; PBMC=peripheral blood mononuclear cell; Pre=predose; SCR=screening; SFU=safety follow-up; CCI; UNS=unscheduled.

- The screening period must be completed within 21 days of signing informed consent.
- For combination therapy, sampling time points relate to the GEN1055 infusion.
- All subjects must provide a biopsy. A fresh biopsy taken during the screening period is preferred, unless medically unfeasible and reviewed and approved by the sponsor. If this cannot be provided, a biopsy taken after failure/stop of last prior treatment and taken within 6 months prior to C1D1 may be provided.
- Subjects must also have on-treatment tumor biopsies performed at any time between C2D8 and C3D1 (both inclusive, ie, after 2 doses of GEN1055 or GEN1055+pembrolizumab), unless medically unfeasible and reviewed and approved by the sponsor.
- Optional.
- Collect at even cycle numbers.
- Only in C1.

1.3.2 Expansion

Table 1-4 Expansion: Schedule of Activities

Trial Period	SCR ^a	Treatment Period ^b								Post-Treatment				UNS ^c	Section	Notes
Cycle/Visit		C1-C2				C3-C4			C5+	EoT ^d	SFU1 ^e	SFU2 ^f	SvFU ^g			
Cycle Day		D1	D3	D8	D15	D1	D8	D15	D1							
Visit Window (days)		+3 ^h	±1	±1	±1	±3	±1	±1	±3							
General and Safety Assessments																
Informed consent	X														10.1.6	Must be obtained prior to the screening period
Demographics	X														8.1.1	
Diagnosis and disease status	X														8.1.2	
Medical history	X														8.1.3	
Eligibility criteria	X														5	
ECOG PS	X	X								X	X			X	8.3.5	
Prior anticancer therapy	X														6.7.1	
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X		X	6.7	
Full physical exam	X	X				X			X	X	X			X	8.3.1	
Brief physical exam				X	X		X	X								Performed as indicated by the subject's symptoms, adverse events, or other findings as determined by the investigator.
Vital signs	X	X		X	X	X	X*	X*	X	X	X	X		X	8.3.3	X* For C3 through C4, the D8 and D15 assessments should only be performed as indicated by the subject's symptoms, adverse events, or other findings as determined by the investigator.
AEs	X*	X	X	X	X	X	X	X	X	X	X	X	X [#]	X	8.4	X*: AEs related to protocol-mandated procedures X#: No monitoring required, but if investigator becomes aware of a treatment-related SAE, it must be reported.
Height	X														8.3.2	
Weight	X	X				X			X	X	X	X				
12-lead ECG	X	See Table 1-6													8.3.4	

Table 1-4 Expansion: Schedule of Activities

Trial Period	SCR ^a	Treatment Period ^b								Post-Treatment				UNS ^c	Section	Notes
Cycle/Visit		C1-C2				C3-C4			C5+	EoT ^d	SFU1 ^e	SFU2 ^f	SvFU ^g			
Cycle Day		D1	D3	D8	D15	D1	D8	D15	D1							
Visit Window (days)		+3 ^h	±1	±1	±1	±3	±1	±1	±3							
Prebaseline imaging scans	X															
Prebaseline labs	X													8.3.6		
Subsequent anticancer therapy										X	X	X	X			
Subject disposition	X									X					Will also be recorded at end of trial.	
Survival status													X	7.1.3		
Local Laboratory Assessments (see Table 8-1 for specific analytes)																
Hepatitis/viral serology	X*,#													8.3.6	* Includes HBV, HCV, HTLV-1, HIV. Only performed if required by local regulations. X [#] All local laboratory samples at the screening visit must be obtained within 7 days prior to C1D1 (with the exception of hepatitis B and C sample, which may be obtained earlier). Screening samples can replace C1D1 if taken within 3 days prior to C1D1. X [*] : Serum pregnancy test required. Additionally, a urine or serum test should be performed within 24 hours of dosing at the start of each subsequent cycle. If a urine pregnancy test is positive, a serum pregnancy test is required to confirm. X [†] Local laboratory samples should be obtained within 3 days before trial treatment administration on Day 1 of each cycle. Laboratory values should be reviewed before dosing.	
Endocrine/Thyroid function	X [#]									X						X
Pregnancy test (serum/urine)	X*,#	X [*]				X [*]			X [*]	X	X	X				X
Hematology	X [#]	X [†]	X	X	X	X [†]	X	X	X [†]	X	X	X				X
Biochemistry	X [#]	X [†]	X	X	X	X [†]	X	X	X [†]	X	X	X				X
Urinalysis	X [#]	X [†]				X [†]			X [†]	X						X
Central Laboratory Assessments																
Tumor biopsy	See Table 1-7													8.6.2		
GEN1055 PK	See Table 1-6													8.5		
GEN1055 ADA	See Table 1-6													8.7		

Table 1-4 Expansion: Schedule of Activities

Trial Period	SCR ^a	Treatment Period ^b								Post-Treatment				UNS ^c	Section	Notes
Cycle/Visit		C1-C2				C3-C4			C5+	EoT ^d	SFU1 ^e	SFU2 ^f	SvFU ^g			
Cycle Day		D1	D3	D8	D15	D1	D8	D15	D1							
Visit Window (days)		+3 ^h	±1	±1	±1	±3	±1	±1	±3							
Biomarkers	See Table 1-7												8.6			
Disease-Specific Assessments																
Imaging/disease assessments	X	See Section 8.2												X	8.2	

Table 1-4 Expansion: Schedule of Activities

Trial Period	SCR ^a	Treatment Period ^b								Post-Treatment				UNS ^c	Section	Notes
Cycle/Visit		C1-C2				C3-C4			C5+	EoT ^d	SFU1 ^e	SFU2 ^f	SvFU ^g			
Cycle Day		D1	D3	D8	D15	D1	D8	D15	D1							
Visit Window (days)		+3 ^h	±1	±1	±1	±3	±1	±1	±3							
Trial Treatment Administration																
EC1																
GEN1055		X				X			X						6	
Pembrolizumab		For subjects with confirmed radiologic progression, pembrolizumab may be administered Q3W														
EC2																
GEN1055		X				X			X						6	
Pembrolizumab		X				X			X							
EC3																
GEN1055		X				X			X						6	
Pembrolizumab		X				X			X							
Pemetrexed		X				X			X							
Option 1: Cisplatin		X				X										
Option 2: carboplatin		X				X										
EC4																
GEN1055		X				X			X						6	
Pembrolizumab		X				X			X							
Carboplatin		X				X										
Option 1: Paclitaxel		X				X										
Option 2: Nab-paclitaxel		X		X	X	X	X	X								

Table 1-4 Expansion: Schedule of Activities

Trial Period	SCR ^a	Treatment Period ^b								Post-Treatment				UNS ^c	Section	Notes				
Cycle/Visit		C1-C2				C3-C4			C5+	EoT ^d	SFU1 ^e	SFU2 ^f	SvFU ^g							
Cycle Day		D1	D3	D8	D15	D1	D8	D15	D1											
Visit Window (days)		+3 ^h	±1	±1	±1	±3	±1	±1	±3								-	±7	±7	±14
EC5																				
GEN1055		See Table 1-5										6								
Pembrolizumab																				
<i>Option 1:</i> Paclitaxel																				
<i>Option 2:</i> Nab-paclitaxel																				
<i>Option 3:</i> Gemcitabine+ carboplatin																				

ADA=anti-drug antibody; AE=adverse event; C=cycle; D=day(s); ECG=electrocardiogram; EC=expansion cohort; ECOG PS=Eastern Cooperative Oncology Group performance status; EoT=end of treatment; HBV=hepatitis B virus; HCV=hepatitis C virus; HTLV-1=human T-lymphotropic virus type 1; PK=pharmacokinetic(s); SAE=serious adverse event; SCR=screening; SFU=safety follow-up; SvFU=survival follow-up; UNS=unscheduled.

- The screening period must be completed within 21 days of signing informed consent.
- During the treatment period, all assessments are to be performed prior to trial treatment administration unless otherwise indicated.
- Unscheduled visits may be performed at any time per investigator's discretion. Assessments should be performed as clinically indicated.
- The EoT assessments should be performed as soon as possible after discontinuation of trial treatment and before the start of subsequent therapy.
- The SFU1 visit should be performed 30 (±7) days after last dose of trial treatment or before the start of subsequent therapy, whichever comes first.
- The SFU2 visit should be performed 90 (±7) days after last dose of trial treatment or before the start of subsequent therapy, whichever comes first.
- Survival status will be assessed every 12 weeks (±14 days), beginning from the day the subject receives the last trial treatment administration and continuing until the subject dies, withdraws consent, the subject is lost to follow-up or the trial ends (see Section 7.1.3 for further details). The SvFU can take place at the same time as the SFU2.
- Visit window (+3d) applies to C2D1 only.

Table 1-5 EC5 Trial Treatment Administrations

													Section	
Cycle	1, 5, 9, 13			2, 6, 10, 14			3, 7, 11, 15			4, 8, 12, 16				
Week	1	2	3	4	5	6	7	8	9	10	11	12		
GEN1055	X			X			X			X			6	Notes
Pembrolizumab	X			X			X			X				
<i>Option 1:</i> Paclitaxel	X	X	X		X	X	X		X	X	X			
<i>Option 2:</i> Nab-paclitaxel	X	X	X		X	X	X		X	X	X			
<i>Option 3:</i> Gemcitabine+ carboplatin	X	X		X	X		X	X		X	X			

C=cycle; EC=expansion cohort; SoC=standard of care.

Table 1-6 Expansion: Schedule of ECG, Vital Signs, Pharmacokinetics, Immunogenicity

Cycle/Visit	SCR ^a	C1-C2							C3-C4					C5+			EoT	SFU1	SFU2	UNS
Cycle Day		D1				D3	D8	D15	D1			D8	D15	D1						
Hours after dose ^b		Pre	EoI	2h	6h	48h	168h	336h	Pre	EoI	2h	168h	336h	Pre	EoI	2h				
Assessment window			+15m	±30m	±1h	±1d	±1d	±1d		+15m	±30m	±1d	±1d		+15m	±30m				
ECG ^c	X	X ^d	X	X					X	X ^e				X	X ^e		X	X	X	X ^e
Vital signs	X	X ^d	X	X			X	X	X		X	X ^f	X ^f	X		X	X	X	X	X ^e
GEN1055 PK		X	X	X ^g	X ^g	X	X	X	X	X	X ^h	X ^h	X ^h	X	X ⁱ		X	X	X	X ^e
GEN1055 ADA		X							X					X ^j			X			

ADA=anti-drug antibody; C=cycle; D/d=day(s); ECG=electrocardiogram; EoI=end of infusion; EoT=end of treatment; h=hour(s); m=minutes; PK=pharmacokinetic(s); Pre=predose; SCR=screening; SFU=safety follow-up; UNS=unscheduled.

- The screening period must be completed within 21 days of signing informed consent.
- For combination therapy, sampling time points relate to the GEN1055 infusion.
- ECGs are to be taken as single assessments. From C5, ECGs must be obtained at C5, C7, and every 4 cycles thereafter (ie, C11, C15, etc). ECGs are to be submitted for central analysis.
- For combination therapy, both before GEN1055 and before pembrolizumab administrations.
- Optional. For ECGs: as clinically indicated
- For C3 through C4, the D8 and D15 assessments should only be performed as indicated by the subject's symptoms, adverse events, or other findings as determined by the investigator.
- Cycle 1 only.
- Cycle 3 only.
- Up to C12.
- Up to C12 at even-numbered cycles only.

Table 1-7 Expansion: Schedule for Biomarker Assessment

Cycle/Visit	SCR ^a	C1-C2					C3				C4+	EoT	UNS
Cycle Day		D1		D3	D8	D15	D1	D8	D15	D1			
Hours after dose ^b		Pre	6h	48h			Pre			Pre			
Visit window			±1h	±1d									
Tumor Biopsy	X ^c					X ^d							X ^e
Soluble Factors (eg, cytokines)		X	X	X	X								X ^e
Immunophenotyping (Whole Blood, PBMCs); CCI		X		X	X	X	X	X	X	X ^f	X	X	X ^e
CCI		X					X			X ^f	X	X	X ^e
Whole blood for DNA control	X												

C=cycle; CCI; D/d=day(s); EoI=end of infusion; EoT=end of treatment; h=hour(s); m=minutes; PBMC=peripheral blood mononuclear cell; Pre=predose;
SCR=screening; SFU=safety follow-up; CCI; UNS=unscheduled

- The screening period must be completed within 21 days of signing informed consent.
- For combination therapy, sampling time points relate to the GEN1055 infusion.
- All subjects must provide a biopsy. A fresh biopsy taken during the screening period is preferred., unless medically unfeasible and reviewed and approved by the sponsor. If this cannot be provided, a biopsy taken after failure/stop of last prior treatment and taken within 6 months prior to C1D1 may be provided.
- Subjects should also have on-treatment tumor biopsies performed at any time between C2D8 and C3D1 (both inclusive, ie, after 2 doses of GEN1055 or GEN1055+pembrolizumab), unless medically unfeasible and reviewed and approved by the sponsor.
- Optional.
- Collect at even cycle numbers.

2 INTRODUCTION

2.1 Trial Rationale

Despite robust and occasionally long-lasting responses in patients with solid malignant tumors treated with immune CPIs, the majority of patients show either primary or acquired resistance to immune checkpoint blockade (Fares et al., 2019). Hence, there is a strong unmet medical need to develop new efficacious therapies for patients with advanced solid cancers whose disease no longer responds to such currently available therapies. A significant factor in the resistance to CPI therapies is the lack of tumor-specific T-cell responses, which may be attributed to low levels of neoantigens, inefficient antigen processing and presentation, and poor T-cell priming. Therefore, combination with agents that enhance these processes may improve outcomes (Jenkins et al., 2018; Nowicki et al., 2018).

OX40 is a co-stimulatory molecule mainly expressed on activated T cells. Upon activation of naïve T cells via **CCl** engagement, OX40 expression is induced and the interaction with its ligand OX40L improves the activation, memory formation, proliferation, and survival of T cells. GEN1055/BNT315 (HexaBody-OX40), which is jointly developed by Genmab and BioNTech, is a hexamerization-enhanced, Fc-silenced IgG1 antibody targeting OX40. Upon binding to cell surface-expressed OX40, it promotes OX40 receptor clustering on the cell surface, which results in FcγR-independent agonistic signaling. This mode of action differentiates GEN1055 from other OX40 antibodies tested in the clinic that are Fc-active and may rely on Fc-FcγR mediated crosslinking to initiate OX40 signaling.

In nonclinical studies, GEN1055 showed the capacity to induce OX40-signaling in OX40-expressing reporter cells in the absence of FcγR-expressing cells and to enhance CD4+ and CD8+ T-cell proliferation, activation and cytokine secretion in healthy donor-derived PBMC samples in vitro. Moreover, GEN1055 showed the capacity to activate CD4+ and CD8+ T cells in vivo in a murine tumor model, concomitant with an increase of the percentage of proliferating and antigen-specific CD8+ T cells and a significant delay in tumor outgrowth. In vivo studies in tumor-free SCID mice revealed that GEN1055 had a PK profile comparable to that of wild-type IgG1 antibodies.

OX40 agonists have demonstrated preliminary clinical activity and were well tolerated as monotherapy, making them attractive combination partners (Section 2.2.2.2). Combination strategies that target T-cell co-stimulation molecules across multiple immune pathways may enhance tumor responses to checkpoint blockade. Since OX40 is often co-expressed on PD-1+ cells, blockade of PD-L1/PD-1 signals and co-stimulation through OX40 may synergize to enhance T-cell effector functions and improve the duration of the response. Thus, it is hypothesized that the combination of GEN1055 and pembrolizumab may elicit a better antitumor immune response than either of the antibodies alone due to additive or synergistic effects of the combination and activation of diverse immunological pathways.

In nonclinical studies, a combination treatment consisting of GEN1055 and the PD-1–blocking antibody pembrolizumab synergistically enhanced CD4+ and CD8+ T-cell proliferation and potentiated cytokine secretion in healthy donor-derived PBMC samples. Moreover, the combination enhanced antigen-specific CD8+ T-cell activation in vitro compared to treatment with GEN1055 alone or with a combination of pembrolizumab and a nonbinding control antibody.

The purpose of this phase 1/2a trial is to characterize the safety, tolerability, PK and pharmacodynamic profiles, and assess preliminary antitumor activity of GEN1055 as both monotherapy and in combination in subjects with malignant, non-CNS, primary solid tumors who have metastatic or advanced disease. Provided that the safety profile of GEN1055 monotherapy is acceptable, the safety and efficacy of GEN1055 in combination with PD-1–blocking antibody pembrolizumab will also be explored. A subsequent expansion part will further evaluate safety and serve to establish a preliminary assessment of efficacy of both monotherapy and combination therapy in selected indications.

2.2 Background

2.2.1 Disease Background

A ranking of indications was based on the composite score of OX40 mRNA expression and expression of T-cell infiltration signatures, as performed in silico across 16 solid tumor indications obtained from the CCI database (version 23Q1 available at Genmab; CCI) and across 31 solid tumor indications available in the TCGA database.

2.2.1.1 CCI

CCI

CCI

CCI [REDACTED]

CCI [REDACTED]

2.2.1.2 CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

2.2.1.3 CCI [REDACTED]

CCI [REDACTED]

CCI

CCI

CCI

CCI

2.2.2 *GEN1055 Background*

Several OX40-targeting mAbs are being developed, or have been in development, which share the feature that they are based on a regular wild-type IgG1 or IgG2 antibody format (eg, GSK3174998, PF-04518600, pogalizumab, BMS-986178 ([Yadav and Redmond, 2022](#))). The OX40 receptor, being part of the TNFRSF, requires multimeric clustering of the receptor molecules on the T-cell surface to induce downstream signaling ultimately leading to T-cell activation, proliferation and survival.

Regular OX40-targeting IgG antibodies in clinical development rely on the interaction with FcγRs expressed by non-T cells, such as macrophages, to induce clustering of the OX40 receptor and downstream activation. The number of cells expressing FcγRs and the level of cellular FcγRs expression itself may be limiting factors in the tumor microenvironment. Moreover, unwanted Fc-mediated target crosslinking and effector functions, such as elimination of proinflammatory OX40-expressing T cells by ADCC, ADCP, or CDC might negatively influence antitumor efficacy.

GEN1055 is a humanized OX40-targeting monoclonal IgG1 antibody designed to increase antitumor T-cell immunity through OX40 agonism. By the addition of a hexamerization-enhancing mutation and an Fc-silencing mutation in the Fc domain of GEN1055, clustering of antibody-bound OX40 molecules on the T-cell surface can be enhanced independently of Fc:FcγR interactions, leading to enhanced T-cell activation. The format of GEN1055 enables more efficient clustering of OX40 receptors and stronger T-cell activation than regular mAbs.

GEN1055 is being developed as a therapeutic agent for the treatment of solid cancers known to express OX40 to offer a better benefits risk balance than currently approved products or combination therapies. The MoA of GEN1055 supports the idea that GEN1055 is a promising therapeutic agent with potential antitumor effects in many different cancer types.

2.2.2.1 *Nonclinical Summary*

A nonclinical data package, consisting of nonclinical pharmacology, PK, and toxicology studies, both in vitro and in vivo, is available for GEN1055.

GEN1055 bound to human OX40 with K_D values in the low nanomolar range, as determined by BLI. Dose-dependent binding to activated CD4+ and CD8+ T cells was confirmed by flow cytometry.

GEN1055 enhanced the activation and proliferation of both CD4+ and CD8+ T cells, as well as the percentage of central memory T cells in in vitro T-cell proliferation assays using healthy donor PBMCs. Within this assay, the proliferation of CD8+ T cells was shown to be dependent on the presence of CD4+ T cells. Increased proliferation was also observed when antigen-specific CD8+ T cells, that were electroporated with OX40, were incubated with GEN1055. Soluble OX40, which could act as a potential sink, was shown to only interfere with the capacity of GEN1055 to induce T-cell proliferation at much higher concentrations than those expected in sera of GEN1055-treated patients.

A combination treatment of GEN1055 and PD-1–blocking antibody pembrolizumab synergistically increased CD4+ and CD8+ T-cell proliferation in polyclonal stimulated healthy donor PBMC samples in vitro. These observations were associated with an increase in cytokine secretion, such as $TNF\alpha$, IL-6, IL-10, and $IFN\gamma$. Upon incubation of antigen-specific CD8+ T cells that were electroporated with OX40 and PD-1, with the combination of GEN1055 and pembrolizumab, an increase in proliferation was observed as compared to treatment with GEN1055 alone or with a combination of pembrolizumab and a nonbinding control antibody. Furthermore, in a mixed-lymphocyte reaction assay, it was shown that the combination of GEN1055 and pembrolizumab resulted in increased secretion of cytokines and other soluble factors, such as IL-2, granulysin, GM-CSF, $TNF\alpha$, and sOX40 compared with either of the antibodies alone.

GEN1055 was designed to prevent Fc-mediated target crosslinking and effector functions, such as ADCC, ADCP, and CDC. The inertness of the Fc domain was characterized in vitro by assessment of complement binding, and Fc γ R binding. Complement factor C1q showed no binding to GEN1055-opsonized activated OX40+ T cells. In addition, no fluid-phase complement activation was observed, indicating that GEN1055 does not activate the complement system in solution. Binding of the Fc domain of GEN1055 to human Fc γ Rs was shown to be abrogated, except for residual binding to Fc γ R1a. Binding to human Fc γ R1a was shown to be very weak, and only observed under specific, highly sensitive, assay conditions. As no binding of GEN1055 was observed to cells transfected to overexpress human Fc γ R1a or in vitro differentiated Fc γ R1a-positive human macrophages, it was concluded that the observed Fc γ R1a binding was not of physiological relevance.

In silico and in vitro analyses did not indicate an enhanced risk of immunogenicity for GEN1055, compared to other therapeutic antibodies that were found to be non-immunogenic in the clinic. In vivo experiments were conducted to study the PK properties of GEN1055 in

tumor-free SCID mice, and antitumor efficacy of GEN1055 in murine tumor models. The in vivo PK characteristics of GEN1055 were comparable to regular IgG1 antibodies. Using the murine MC38 colon tumor model in immunocompetent human OX40 knock-in mice, GEN1055 was shown to significantly inhibit tumor progression, which was associated with pharmacodynamic changes observed in the peripheral blood of these mice.

CCI [REDACTED] ADA in toxicology species is common with human antibodies and is not predictive of clinical immunogenicity (EMA, 2012; FDA, 2014). In addition, GEN1055-related transitory changes in hematology parameters were observed including mild to moderately decreased RBC, hematocrit, hemoglobin, and serum albumin and albumin:globulin ratio, and increased total reticulocyte count, total protein and globulin. CCI [REDACTED]

No genotoxicity, chronic toxicity, carcinogenicity, or reproductive toxicity testing has been conducted.

For additional details regarding nonclinical studies, refer to the GEN1055 IB.

2.2.2.2 *Clinical Summary*

This is the first clinical trial testing GEN1055 in humans; therefore no clinical experience is available. Please refer to the IB for the latest preliminary information.

2.3 **Benefit/Risk Assessment**

2.3.1 *Potential Benefit*

2.3.1.1 *Potential Benefits of GEN1055*

Based on nonclinical data and published data regarding other agents that target human OX40 in various tumor types, clinical antitumor activity can be expected for GEN1055. Therefore, cancer patients with limited treatment options, and for whom the investigator agrees that clinical trial participation is appropriate, may benefit from treatment with GEN1055.

2.3.1.2 *Potential Benefits of GEN1055 in Combination With Pembrolizumab ± Chemotherapy*

Based on their respective MoAs, it is hypothesized that the combination of GEN1055 with pembrolizumab will enhance the antitumor activity as compared with pembrolizumab or GEN1055 therapy separately (Section 2.2.2).

2.3.2 *Potential Risks*

2.3.2.1 *Potential Risks of GEN1055*

GEN1055 has not been administered to human subjects; therefore, no clinical data are available. The assessment of potential side effects of GEN1055 is based on nonclinical studies conducted to date, and the literature for other OX40-binding compounds.

In a 5-week GLP repeat dose toxicity study in cynomolgus monkeys (Section 2.2.2.1), GEN1055-related changes in hematology parameters were transient and returned to normal after a 4-week recovery period. CCI

Targeting OX40 has not in itself led to unacceptable toxicities or safety concerns with other compounds in clinical development (see Section 2.3.3).

Risk mitigation strategies are provided in Sections 6.8.2 through 6.8.4 and summarized in Section 2.3.4.

Refer to the GEN1055 IB for further details.

2.3.2.2 *Potential Risks of GEN1055 in Combination With Pembrolizumab ± Chemotherapy*

GEN1055 and pembrolizumab are both immunomodulatory agents. Therefore, overlapping toxicities with GEN1055 and pembrolizumab are anticipated to include irAEs and IRRs.

Pembrolizumab is most commonly associated with immune-related adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, and skin reactions). Most of these, including severe reactions, resolve following initiation of appropriate medical therapy or withdrawal of pembrolizumab (KEYTRUDA SmPC, 2023).

The most common adverse reactions (reported in $\geq 20\%$ of patients) were:

- pembrolizumab as a single agent: fatigue, musculoskeletal pain, rash, diarrhea, pyrexia, cough, decreased appetite, pruritus, dyspnea, constipation, pain, abdominal pain, nausea, and hypothyroidism (KEYTRUDA US PI, 2023).
- pembrolizumab in combination with chemotherapy (including carboplatin, cisplatin, paclitaxel, nab-paclitaxel and gemcitabine): fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, stomatitis, headache, weight loss, abdominal pain, arthralgia, myalgia, and insomnia (KEYTRUDA US PI, 2023).

The release of tumor antigens from chemotherapy could potentially contribute to a boost of the immune responses of GEN1055 and pembrolizumab and thereby potentially add to the risk or severity of irAEs.

2.3.3 Experience With OX40-Targeting Drugs

To date, several OX40-targeting mAbs are, or have been, in clinical development for the treatment of solid tumors. Regular IgG antibody-based compounds (eg, BMS-986178, GSK-3174998, PF-04518600, MEDI-0562, INCAGN1949, and vonlerlizumab/MOXR0916) were generally well tolerated when administered as monotherapy. Most common AEs that were reported included fatigue, rash, nausea, diarrhea, and IRRs (Davis et al., 2022; Diab et al., 2022; Glisson et al., 2020; Gutierrez et al., 2021; Kim et al., 2022; Lee, 2021). In addition, lymphopenia and decreased lymphocyte count were reported (Curti et al., 2013; Kim et al., 2022). Upon combining such mAbs with CPI treatment (such as pembrolizumab, nivolumab, atezolizumab, or durvalumab), a modest increase in the incidence of treatment-related AEs was generally reported. The most common AEs reported for combination treatments included fatigue, pruritus, rash, pyrexia, diarrhea, anemia, decreased appetite, and IRRs (Goldman et al., 2022; Gutierrez et al., 2021; Hamid et al., 2022; Lee, 2021). In addition, lymphopenia and decreased lymphocyte count were reported (Gutierrez et al., 2021; Hamid et al., 2022). The clinical efficacy observed so far for regular IgG-based OX40 monotherapies is generally considered limited, while this efficacy may be enhanced to a varying extent by combining with any of the mentioned CPI treatments.

An OX40-targeting agent, INBRX-106, that aims to multimerize the OX40 receptor on the cell surface (ie, with a similar MoA as hypothesized for GEN1055, but with a wild-type Fc domain) was also well tolerated when administered either as monotherapy or in combination with pembrolizumab, with mostly mild or moderate immune-related toxicities (Inhibrx, 2021b; Inhibrx, 2022; Rowell et al., 2021). Signs of clinical efficacy were reported for INBRX-106, based on a limited set of evaluable patients (CPI-naïve nasopharyngeal carcinoma, and uveal and cutaneous melanoma) in interim analyses.

For a more extensive overview of clinical experiences with OX40-targeting therapies, please refer to the GEN1055 IB.

2.3.4 Conclusion

Based on the interpretation of the nonclinical data available to date, published data from other OX40-targeting agents, the conduct of this trial investigating GEN1055 monotherapy and GEN1055+pembrolizumab with or without chemotherapy is regarded as justifiable.

A cautious approach will be applied in this FIH trial with dose escalation starting at the lower end of the pharmacologically-active dose range, with strict DLT criteria, adequate AE management, and safety stopping rules in place (see Section 6.8).

The population eligible for the cohorts with dose escalation of this trial represents subjects with selected malignant solid tumors, who have failed available standard therapy or who are not candidates for standard therapy, and for who, in the opinion of the investigator, experimental therapy with GEN1055 or GEN1055+pembrolizumab with or without chemotherapy may be beneficial.

Events to be closely monitored for GEN1055 include irAEs and IRRs. The DEC and the Safety Committee will closely monitor subject safety as described in Section 10.1.8.

Subjects enrolled will have frequent visits and will be monitored closely by site staff and via medical monitoring throughout the trial. An elaborate risk mitigation plan for handling potential AEs has been prepared (and will be updated for phase 1b as deemed necessary) in order to manage AEs, delay the dose, or discontinue treatment based on AEs that may occur with GEN1055 and pembrolizumab (Sections 6.8.2 through 6.8.4). The anticipated combined safety profile will be carefully assessed prior to the start of the combination therapy dose escalation phase 1b with focus on potentially overlapping toxicities.

All subjects enrolled in this trial will be followed and monitored by qualified health care professionals who will provide care and closely evaluate each subject's response to GEN1055 and GEN1055+pembrolizumab ± chemotherapy both in terms of safety profile and efficacy.

Collectively, the benefit/risk ratio is considered favorable for trial GCT1055-01.

For further details on GEN1055, refer to the IB.

3 OBJECTIVES AND ENDPOINTS

Table 3-1 Objectives and Endpoints – Dose Escalation Phase 1a and 1b

Objectives	Endpoints
Primary	
Evaluate the safety of GEN1055 as monotherapy and as combination therapy with pembrolizumab	Incidence and severity of AEs
Determine expansion doses of GEN1055 as monotherapy and as combination therapy with pembrolizumab	Incidence of DLTs
Secondary	
Characterize the PK properties of GEN1055 as monotherapy and as combination therapy with pembrolizumab	PK parameters for GEN1055: - C_{max} - t_{max} - C_{trough} - AUC_{0-1ast} - AUC_{0-inf} - t_{1/2} - CL
Evaluate immunogenicity of GEN1055	ADA response to GEN1055 as monotherapy and as combination therapy with pembrolizumab
Assess the antitumor activity of GEN1055 as monotherapy and as combination therapy with pembrolizumab	According to RECIST v1.1 as assessed by investigator: - ORR - DoR - TTR - DCR
Exploratory	
Explore the pharmacodynamics, potential response, and safety biomarkers for GEN1055 as monotherapy and as combination therapy with pembrolizumab	- Immune system activation, expression of the target and molecules of interest and changes in CCI over time - OX40 receptor occupancy before and after treatment with GEN1055
Explore efficacy of GEN1055 as monotherapy and as combination therapy with pembrolizumab	- PFS according to RECIST v1.1 as assessed by investigator - OS
Explore immunotherapy antitumor activity of GEN1055 as monotherapy and as combination therapy with pembrolizumab	According to iRECIST as assessed by investigator: - iORR - iDCR - iDoR
Explore preliminary immunotherapy efficacy of GEN1055 as monotherapy and as combination therapy with pembrolizumab	iPFS according to iRECIST as assessed by investigator
To assess tumor size change with GEN1055 as monotherapy and as combination therapy.	Change in tumor size

Table 3-2 Objectives and Endpoints – Expansion

Objectives	Endpoints
Primary	
Assess the antitumor activity of GEN1055 as monotherapy and as combination therapy	According to RECIST v1.1 as assessed by investigator: ORR
Secondary	
Assess the antitumor activity of GEN1055 as monotherapy and as combination therapy	According to RECIST v1.1 as assessed by investigator: - DoR - TTR - DCR
Assess the antitumor efficacy of GEN1055 as monotherapy and as combination therapy	- PFS according to RECIST v1.1 as assessed by investigator - OS
Evaluate safety of GEN1055 as monotherapy and as combination therapy	Incidence and severity of AEs
Evaluate immunogenicity of GEN1055 as monotherapy and as combination therapy	ADA response to GEN1055 as monotherapy and as combination therapy
Characterize the PK of GEN1055 as monotherapy and in combination therapy	PK parameters for GEN1055: - C_{max} - t_{max} - C_{trough} - AUC_{0-tlast} - AUC_{0-inf} - t_{1/2} - CL
Exploratory	
Explore immunotherapy antitumor activity of GEN1055 as monotherapy and as combination therapy	Antitumor activity according to iRECIST as assessed by investigator: - iORR - iDCR - iDoR
Explore immunotherapy efficacy of GEN1055 as monotherapy and as combination therapy	According to iRECIST as assessed by investigator: iPFS according to iRECIST
Explore the pharmacodynamics, potential response, and safety biomarkers for GEN1055 as monotherapy and as combination therapy	Immune system activation, expression of the target and molecules of interest and changes in CCI over time
To assess tumor size change with GEN1055 as monotherapy and as combination therapy.	Change in tumor size

4 TRIAL DESIGN

4.1 Description of Trial Design

This is a phase 1/2a open-label, multicenter, multinational trial in subjects with malignant, primary solid tumors who have metastatic or advanced disease to evaluate the tolerability, PK and pharmacodynamic profiles, and assess preliminary antitumor activity of trial treatment. A diagram of the trial design is provided in Section 1.2.

Assessments will be performed as detailed in the Schedule of Activities, Section 1.3. Trial treatment will be administered by IV infusion (see Section 6). Treatment for a subject should continue until the subject fulfills 1 of the treatment discontinuation criteria discussed in Section 7.1.

The trial consists of escalation (phase 1a/1b) and expansion (phase 2a) parts as follows:

- Phase 1a: dose escalation with GEN1055 as monotherapy (approximately 50 subjects)
- Phase 1b: dose escalation with GEN1055 in combination with a fixed dose of pembrolizumab (GEN1055+pembrolizumab) (approximately 40 subjects)
- Phase 2a: expansion
 - CCI [REDACTED]
 - CCI [REDACTED]
 - CCI [REDACTED]
 - CCI [REDACTED]
 - CCI [REDACTED]

Each part will consist of:

- Screening (up to 21 days prior to C1D1)
- A treatment period (from C1D1 until discontinuation of trial treatment)
- A first safety follow-up visit 30 days after the last dose of trial treatment
- A second safety follow-up visit 90 days after the last dose of trial treatment
- Survival follow-up starting after the last safety follow-up visit

Approximately 270 subjects will be enrolled in this trial.

In the Dose escalation part, subjects who are not DLT-evaluable (see Section 9) may be replaced. These replacement subjects will be assigned to the same treatment cohort as the subjects they are replacing. In the expansion part, subjects who discontinue from the trial will not be replaced, except if not DLT evaluable during the safety run-in period (see Section 4.1.3).

If more than 1 GEN1055 dose regimen is chosen for any of the phase 2a ECs based on data from phase 1a or 1b, symmetrical randomization within each EC will be used to avoid bias in

the assignment of subjects to treatment dose regimen groups. Refer to Section 6.5 for further details regarding randomization and stratification.

A Safety Committee and a DEC will be commissioned for this trial. The committees structure is detailed in Section 10.1.8.

The protocol may be amended to explore additional indication, doses/schedules and combination compounds both during dose escalation and/or in separate ECs based on emerging data. Any such amendment(s) will be submitted as a substantial amendment prior to initiation.

4.1.1 Phase 1a – Dose Escalation (GEN1055 Monotherapy)

In the Monotherapy dose escalation phase 1a, GEN1055 will be evaluated in metastatic or advanced malignant solid tumors. At each DL, DLTs will be assessed in the first treatment cycle, ie, a DLT evaluation period of 21 days from C1D1.

GEN1055 will be evaluated at approximately 6 main DLs ranging from CCI administered Q3W including, but not limited to, those described in Section 1.2. As nonmonotonous dose-response relationships have been observed with prior clinical OX40-targeting antibodies, intermediate dose levels may be considered to identify the optimal dose, (if needed) using a BOIN design with a target toxicity rate of 0.30 (Liu and Yuan, 2015). Intermediate DLs of CCI are considered, unless data gathered in dose escalation suggest more appropriate intermediate DLs. Intra patient dose escalation is not allowed.

There will be a minimum of 2 nights between the first and second subject at each DL to account for any acute safety signals. An overnight stay will be required for the first subject at each DL and may be required for additional subjects. Furthermore, no subjects within a cohort will receive their first treatment simultaneously, ie, on the same day during dose escalation except for DLs declared safe by the Safety Committee which are further investigated by backfilling.

The DLT rate for a given DL is estimated as total number of DLTs/total number of subjects treated and qualifying for the DDS (at that DL). Based on the accrued data (at each DL), the mBOIN decision guidance rules are supplied in Table 4-1.

Table 4-1 Modified BOIN Decision Guidance Rules

	Total Number of Subjects Treated at a DL	3	4	5	6	7	8	9
Decision Based on Total Number of DLTs at the DL	Escalate if # DLT	0	0	≤ 1	≤ 1	≤ 1	≤ 1	≤ 2
	Remain if # DLT	1	1	NA	2	2	2	3
	De-escalate if # DLT	2	2	2	3	3	3	4
	Terminate a DL if # DLT	3	≥3	≥3	≥4	≥4	≥4	≥5

BOIN=Bayesian optimal interval; DL=dose level; DLT=dose-limiting toxicity; NA=not applicable.

If de-escalation is mandated, the dose will be decreased to the preceding lower main or intermediate DL.

The overall decision process for the next DL and/or to propose the expansion dose or combination start dose or the MTD/MAD is summarized in Section [10.1.8](#).

Once the final monotherapy expansion dose(s)/MTD/MAD has been determined, no further subjects will be enrolled in the monotherapy escalation part (including backfilling).

4.1.1.1 Modifications to BOIN

The BOIN algorithm has been modified to limit number of subjects that can be dosed at a specific DL. The escalation ultimately stops if 9 subjects are already dosed on the proposed DL.

For DLs with 3 DLT-evaluable subjects, the escalation decision will be consistent with the “3+3” design (ie, escalate if no DLT, remain on same dose level if 1 DLT, de-escalate if 2 DLTs, and terminate dose level if 3 DLTs); see [Table 4-1](#).

4.1.1.2 Cohort Size

To limit number of subjects treated with a presumed non-efficacious dose, the first cohort will enroll 1 subject but will be expanded to 3 subjects if a $\geq$ grade 2 AE is observed during Cycle 1, unless clearly related to underlying disease or extraneous cases (eg, broken arm due to fall). Subsequent cohorts will initially enroll at least 3 subjects each.

Additional recruitment will be allowed to ensure 3 DLT-evaluable subjects at each DL with further details provided in the cohort recruitment plan.

4.1.1.3 Stopping Rules

If revisiting a DL where 9 subjects have been dosed, further dose escalation will be stopped.

If it is known a priori before revisiting a DL that the guidance would be to “de-escalate,” that regimen can be terminated (see [Table 4-1](#)).

The MTD/MAD may be declared based on at least 6 subjects if the recommendation is to escalate and the next level is not available or have been terminated.

4.1.1.4 Backfill Cohorts

Backfill subjects are those who are added to a DL after it has been declared as safe by the Safety Committee. More than 1 backfill subject can therefore receive treatment simultaneously in a DL declared safe. Additional subjects may be enrolled to backfill DLs that have been declared safe to better understand the safety, tolerability, PK, pharmacodynamics, or antitumor activity. Additional subjects per DL may be enrolled in this fashion bringing the number of subjects at a DL up to a maximum of 9 subjects.

However, if the mBOIN algorithm later stipulates de-escalation to an over-recruited DL, all DLT-evaluable subjects at the current DL, including any backfilled subjects, will be considered for the BOIN decision recommendation for the next DL.

4.1.1.5 *Other Dose Escalation/De-escalation Procedures*

Escalation to the next DL will not occur until all subjects in a cohort have completed the DLT evaluation period.

See Section 10.1.8 for details on committee governance procedures for dose escalation/de-escalation.

The expansion dose(s) may be declared (with at least 6 subjects on the relevant DL(s)) based on a review of the available safety and dosing information (including AEs, safety laboratory values, pharmacodynamic markers, and any observations made after the end of the DLT evaluation period), and may be lower than the MTD.

ECs may be initiated before the MTD has been reached.

4.1.2 *Phase 1b – Dose Escalation (GEN1055 Combination Therapy)*

GEN1055 will be evaluated at approximately 3 DLs in combination with pembrolizumab (200 mg Q3W). The GEN1055 starting dose will be at least 1 DL lower than a monotherapy DL declared safe in phase 1a. The starting dose decision will also be guided by PK/pharmacodynamic activity. The approach for dose escalation steps will be same to that in phase 1a (see Section 4.1.1). The DL cohorts will initially enroll at least 3 subjects each, with the option to backfill DLs with up to approximately 9 subjects each. Intra patient dose escalation is not allowed.

Once the final combination therapy expansion dose(s)/MTD/MAD has been determined, no further subjects will be enrolled in the combination therapy escalation part (including backfilling).

4.1.3 *Phase 2a – Expansion*

The aim of the expansion part is to provide further data on the safety, tolerability, MoA, PK, and antitumor activity of the selected doses and schedules in separate indication ECs:

- CCI [REDACTED]
CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]

For each EC, more than 1 dose or dose regimen of GEN1055 may be selected based on data from phases 1a and 1b. If more than 1 GEN1055 dose regimen is selected, subjects will be randomized symmetrically between dose regimens within each EC with potential stratification in some ECs.

The combination therapy regimens for EC2, EC3, EC4, and EC5 will be fixed (see Section 6.1) and the ECs may run in parallel or staggered. It is at the sponsor's discretion when each EC is opened.

EC3, EC4, and EC5 will be initiated with a 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 in the first cycle (ie, the DLT period) and the decision guided by Table 4-2. 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 any screening failure of 33%. The decision to further enroll after the safety run-in will take into consideration the totality of information of the trial and will be governed by the DEC and Safety Committee as detailed in Section 10.1.8.

Table 4-2 Decision Table for Safety Run-in in EC3, EC4, EC5

Number of Dose-limiting Toxicities	Number of DL evaluable 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 the safety run-in; DL=dose level; E (blue)=expand enrollment to the full cohort (the regimen is declared safe); EC=expansion cohort; S (yellow)=stay and enroll additional subjects into the safety run-in (unless the Safety Committee endorses to proceed to the full cohort).

Additional indications, doses/schedules and combination compounds may be explored in separate cohorts in the expansion part as data emerges. A substantial amendment will be submitted and subject to approval by health authorities and IRBs/ethics committee prior to initiation of any such additional cohorts.

4.2 Trial Design Rationale

This trial is being conducted to identify the expansion dose(s)/MTD/MAD and to obtain preliminary efficacy and safety of trial treatment in subjects with metastatic or advanced cancer. To this end, the well-established BOIN design is applied in a dose escalation part to determine dose regimen(s) to be further studied (with potential randomization) in ECs in selected indications. These data will be used to inform future clinical development of GEN1055.

EC1 is included to explore the MoA and single agent activity of GEN1055.

Pembrolizumab is approved as monotherapy in CCI [REDACTED] in the EU and US. EC2 is included to explore the potential additive or synergistic effects of GEN1055 and pembrolizumab CCI [REDACTED].

Pembrolizumab is also approved in combination with chemotherapy in the CCI [REDACTED] in the EU and US. EC3 and EC4 are included to explore the combination of GEN1055 with pembrolizumab+chemotherapy as CCI [REDACTED]. EC5 is included to explore the combination of GEN1055 with pembrolizumab+chemotherapy as CCI [REDACTED]. The expansion dose(s) for GEN1055 and pembrolizumab combination therapy will be established in phase 1b before initiating EC2, EC3, EC4, and EC5. To further safeguard subjects, these cohorts will be initiated with a safety run-in.

4.3 Dose and Schedule Rationale

4.3.1 IMP Dose and Schedule Rationale

The FIH starting dose, dose escalation steps, maximum dose and schedule were selected based on careful evaluation of available data on clinical experience of prior OX40 targeting therapies, OX40 expression, in vitro target binding and T-cell proliferation, PK in tumor-free SCID mice and cynomolgus monkeys, antitumor activity in tumor-bearing mice, and observations of safety and pharmacological activity in cynomolgus monkey toxicity studies. Dose and schedule selection were informed by a PBPK model that was developed integrating these sources of information, with the following considerations:

1. Based on published data of clinical experience, OX40 agonist antibodies are observed to be well tolerated in FIH studies. OX40 is expressed on T cells activated via the TCR/CD3 pathway, with higher expression on CD4+ than on CD8+ T cells. Like other OX40 agonists, GEN1055 is involved in the co-stimulation of already activated T cells, which in cancer patients are considered to be located predominantly in the tumor and tumor draining lymph nodes. Lower numbers of activated T cells are expected in other tissues, and even fewer in peripheral blood where exposure is higher than in tissues. The tumor and tumor draining lymph nodes are therefore considered the main sites of pharmacological activity.
2. In vitro assays use coincubation with a CD3 antibody to provide the first activation signal. CCI [REDACTED]
3. Prior OX40-targeting antibodies have demonstrated a non-monotonous dose-response relationship in patients (Inhibrx, 2021a; Rowell et al., 2021; Wang et al., 2019), potentially caused by T-cell exhaustion upon high and prolonged OX40 engagement.

Flat dosing is proposed for use in the GEN1055 FIH trial. Flat dosing is increasingly used for mAb therapeutics as it offers several advantages over weight-based dosing, including convenience of preparation, reduced risk of dosing errors, and reduction of drug waste, and does not necessarily lead to a wider range of exposures (Bai et al., 2012; Wang et al., 2009).

The prior clinical experience with the target, the MoA, and the nonclinical data for GEN1055 support the PAD range as a basis for clinical dose selection. The EC₅₀ for polyclonal T-cell proliferation in vitro was used as a starting point to characterize the lower end of the PAD range in patients. CCI

Estimates based on doses associated with minimal pharmacological effect in mice and cynomolgus monkeys resulted in substantially higher human equivalent doses. The starting dose of CCI is therefore considered sufficiently conservative and warrants a single-subject cohort. The monotherapy dose escalation phase 1a transitions to 3-subject cohorts CCI

CCI

For further details, see the GEN1055 IB.

4.3.2 AMP Dose and Schedule Rationale

The background treatment in combination therapy regimens as described in Section 6.1 is in accordance with the approved indications and lines of therapy in the EU and US.

4.4 Primary Completion Date, Estimated Trial Duration, and End of Trial Definition

4.4.1 Primary Completion Date

The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), whether the trial concluded as planned in the protocol or was terminated early. In the case of clinical trials with more than 1 primary endpoint with different completion dates, this term refers to the date on which data collection is completed for all of the primary endpoints.

Primary completion is anticipated to occur at the same time as the end of trial.

4.4.2 *Estimated Trial Duration*

The estimated maximum trial duration is 38 months after the last enrolled subject's first treatment in the trial.

4.4.3 *Estimated Trial Duration for an Individual Subject*

The estimated trial duration for an individual subject is up to approximately 39 months, consisting of a 21-day screening period, an estimated 24-month treatment period (the duration of treatment may vary for each subject), a 90-day safety follow-up period, and an estimated 11-month survival follow-up period.

A subject is considered to have completed the trial if the subject has completed all periods of the trial including the last contact shown in the Schedule of Activities (Section 1.3).

4.4.4 *End of Trial*

The end of trial is defined as the date of the last contact of the last subject in the trial globally.

5 TRIAL POPULATION

The appropriate written informed consent must be obtained before any trial-specific activities/procedures are performed. After signing the ICF, subjects will be assigned a unique subject identifier before undergoing any screening procedures. Subjects that meet all of the eligibility criteria may be enrolled.

The inclusion and exclusion criteria for enrolling subjects in this trial are described below. If there is a question about these criteria, the investigator must consult with the sponsor and resolve any issues before enrolling a subject in the trial. Waivers are not allowed.

NOTE: Investigators, in coordination with the medical officer (or delegate) must ensure enrollment criteria are met and the eligibility review is completed. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of trial treatment is given, the investigator must ensure the subject fulfills all eligibility criteria prior to first dose.

5.1 Inclusion Criteria

Each subject must fulfill all inclusion criteria in Section 5.1.1 as well as the criteria listed in either Section 5.1.2 (dose escalation) or Section 5.1.3 (expansion) to be enrolled in the trial.

5.1.1 *All Cohorts*

1. Must sign an ICF indicating that the purpose of the trial and the procedures required for the trial are understood and indicating that the subject is willing to participate in the trial. Where required by local or country specific regulations, each subject must sign a separate ICF indicating agreement to provide samples for genomic biomarker analysis (DNA and RNA).
2. Be at least 18 (or the legal age of consent in the jurisdiction in which the trial is taking place) years of age.

3. Have measurable disease according to RECIST v1.1 (see Section 10.6).
4. Provide all pre-baseline scans since failure of last prior therapy (ie, documented radiographic PD), if available.
5. Have ECOG PS score of 0 to 1 at screening and on C1D1 pretreatment. *Note: Do not perform C1D1 ECOG PS if within 3 days of Screening ECOG PS.*
6. A female subject with reproductive potential must agree to use adequate contraception during the trial, and for 6 months after receiving the last dose of GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice. Reproductive potential and adequate contraception (ie, highly effective methods of contraception) are defined in Section 10.3. In countries where 2 forms of highly effective methods of contraception are required, both methods will be required for inclusion.
NOTE: If reproductive potential changes after start of the trial (eg, female with reproductive potential becomes sexually active) a female subject must begin adequate contraception (ie, highly effective methods of contraception), as described in Section 10.3. In countries where 2 forms of highly effective methods of contraception are required, both methods must be initiated.
7. A female subject with reproductive potential must have a negative serum beta-hCG at screening.
8. A female subject must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial and for 6 months after receiving the last dose of GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice.
9. A male subject must agree not to donate sperm during the trial and for 6 months after receiving the last dose of GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice.
10. A male subject who is sexually active with a female with reproductive 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 GEN1055 administration; all males must also refrain from donating sperm during the trial and for 6 months after receiving the last dose of GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice. For Japanese subjects, see also Section 10.10.2.
11. Male subjects (including males who have had vasectomies) whose partner is pregnant should use condoms for the duration of the trial and for 6 months after receiving the last dose of GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice.
12. Is willing and able to adhere to the prohibitions and restrictions specified in this protocol.

13. Has acceptable laboratory test results prior to trial treatment, as follows:

Parameter	Result	
a. GFR	GFR ≥ 45 mL/min/1.73 m ² according to the abbreviated MDRD equation: GFR = $186 \times (\text{SCr} - 1.154) \times (\text{age} - 0.203) \times (0.742 \text{ if female})$, where SCr is expressed in mg/dL and the result is multiplied by 1.212 if the subject is black.	
b. ALT	$\leq 3.0 \times \text{ULN}$	In case of a concomitant alkaline phosphatase level of $> 2.5 \times \text{ULN}$, ALT and AST levels must be $\leq 1.5 \times \text{ULN}$.
c. AST	$\leq 3.0 \times \text{ULN}$	
d. Total bilirubin	$\leq 1.5 \times \text{ULN}$ <i>NOTE: A subject with Gilbert's syndrome may be included if total bilirubin is $\leq 2 \times \text{ULN}$ and direct bilirubin is $\leq 1.5 \times \text{ULN}$.</i>	
e. Hemoglobin	≥ 9 g/dL (≥ 90 g/L or ≥ 5.6 mmol/L) <i>NOTE: Red blood cell transfusion may be administered during Screening to meet this requirement unless subject is chronic transfusion dependent.</i>	
g. Absolute neutrophil count	$> 1.5 \times 10^9/\text{L}$ ($> 1000/\mu\text{L}$) <i>NOTE: Must be met without administration of growth factors within 2 weeks prior to C1D1.</i>	
h. Platelet count	$> 100 \times 10^9/\text{L}$ ($> 100,000/\mu\text{L}$) <i>NOTE: Must be met without administration of platelet transfusion within 2 weeks prior to C1D1.</i>	

14. Provide a biopsy (ie, FFPE slides/block. A fresh biopsy taken during the screening period is preferred), unless medically unfeasible and reviewed and approved by the sponsor. If this cannot be provided, a biopsy taken after failure/stop of last prior treatment and taken within 6 months prior to C1D1 may be provided.

Note: Documentation of biopsy collection and shipment must be submitted to the sponsor as a part of the eligibility package prior to administration of the first dose of trial treatment.

5.1.2 Phases 1a and 1b – Dose Escalation as Monotherapy and as Combination Therapy

In addition to the inclusion criteria listed in Section 5.1.1, each subject must fulfill all of the following inclusion criteria to be enrolled in the escalation part of the trial.

15. Have histologically or cytologically confirmed non-CNS primary solid tumors and have metastatic or advanced disease.
16. Criterion modified per Amendment 1: Have progressed on SoC therapy which should include platinum-based chemotherapy and anti-PD-1/PD-L1 therapies, if applicable for the tumor type, or for whom there is no available standard therapy likely to provide clinical benefit, and for whom experimental therapy with GEN1055 or GEN1055+pembrolizumab may be beneficial, in the opinion of the investigator.

5.1.3 *Part 2a – Expansion*

Each subject must fulfill all of the following inclusion criteria to be enrolled in the expansion part of the trial.

17. Have histologically or cytologically confirmed diagnosis of 1 of the following:

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

18. CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

19. CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]
[REDACTED]

20. CCI [REDACTED]

CCI [REDACTED]
[REDACTED]

CCI [REDACTED]
[REDACTED]

CCI [REDACTED]
[REDACTED]

21. CCI [REDACTED]

CCI [REDACTED]
[REDACTED]

CCI [REDACTED]
[REDACTED]

CCI [REDACTED]
[REDACTED]

22. CCI [REDACTED]

CCI [REDACTED]
[REDACTED]

CCI [REDACTED]
[REDACTED]

CCI

CCI

5.2 Exclusion Criteria

Unless otherwise specified, the below exclusion criteria apply to all parts of this trial.

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

1. Has uncontrolled intercurrent illness, including but not limited to:
 - a. Ongoing or active infection requiring IV treatment with anti-infective therapy administered less than 2 weeks prior to first dose (including COVID-19 infection).
Note: a past COVID-19 infection may be a risk factor, but if resolved and the subject is vaccinated, it may be allowable to enroll the subject.
 - b. Significant cardiovascular impairment including
 - i. Symptomatic congestive heart failure (Class III or IV as classified by the New York Heart Association), unstable angina pectoris, or cardiac arrhythmia.
 - ii. Uncontrolled hypertension defined as systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg, despite optimal medical management.
 - iii. Prolonged QTc interval at baseline of ≥ 470 milliseconds using Fridericia's QT correction formula.
 - c. Ongoing or recent (within 1 year of screening) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for irAEs.
Note: The following condition is not exclusionary: Residual hypothyroidism that requires only hormone replacement.
 - d. History of grade 3 or higher irAEs that led to treatment discontinuation of a CPI. A subject with irAEs below grade 3 that led to discontinuation should be discussed with the sponsor. Grade 3 irAEs that have fully recovered may also be discussed.
 - e. Prior history of myositis, Guillain-Barré syndrome, or myasthenia gravis of any grade.
 - f. History of chronic liver disease (eg, alcoholic hepatitis or NASH), drug-related or autoimmune hepatitis, or evidence of hepatic cirrhosis.
 - g. Evidence of interstitial lung disease.

- h. Ongoing pneumonitis (any grade) including any radiological change of ongoing pneumonitis at baseline or history of noninfectious drug-, immune-, or radiation-related pneumonitis that has required steroids.
 - 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 GEN1055.
 - j. Serious, non-healing wound, skin ulcer (of any grade), or bone fracture.
2. Has been exposed to any of the following prior therapies/treatments within the specified timeframes:
- a. Treatment with an anticancer agent within 4 weeks or for systemic therapies within 5 half-lives of the drug, whichever is shorter, prior to trial treatment administration.
 - b. Condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first treatment. Inhaled or topical steroids, and adrenal or pituitary replacement steroid >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
 - c. Treatment with bisphosphonates (eg, pamidronate, zoledronic acid, etc) and RANK-L inhibitors initiated within 28 days before the first planned dose of trial treatment administration. The initiation of bisphosphonates is also not allowed during the first 4 weeks of trial treatment, unless approved by sponsor.
 - d. Has received G-CSF/GM-CSF support within 2 weeks prior to first trial treatment administration or is chronically transfusion-dependent.
 - e. History of $\geq$ grade 3 allergic reactions to mAb therapy or known or suspected allergy or intolerance to any agent to be given during the course of this trial.
 - f. RT within 14 days before the planned first dose of trial treatment. Palliative RT of bone metastases up to 7 days prior to C1D1 will be allowed.
 - g. Treated with any investigational or non-investigational anticancer agent (including investigational vaccines) or used an invasive investigational medical device within 28 days or 5 half-lives, whichever is shorter, before the planned first dose of GEN1055 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 an investigational agent within 28 days prior to the first GEN1055.*
 - h. Prior treatment with an OX40-targeting agent or another co-stimulatory receptor on T cells.
 - i. **Only for EC1:** Discontinued treatment due to PD within the first 12 weeks of a CPI-containing treatment.

- j. Prior treatment with a T-cell agonist or a CTLA-4-targeting agent within 6 weeks prior to the initiation of treatment.
3. Prior treatment with live, attenuated vaccines within 28 days prior to initiation of GEN1055. 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 nonauthorized SARS-CoV-2 vaccinations are not allowed.
- Note: 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.*
- Note: SARS-CoV-2 vaccine should not be administered during the DLT observation period.*
4. Has clinically significant toxicities from previous anticancer therapies that have not resolved to baseline levels or to grade 1 or lower, except for alopecia, anorexia, vitiligo, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy. Anorexia, hyperthyroidism, hypothyroidism, and peripheral neuropathy must have recovered to grade 2.
5. Any history of intracerebral arteriovenous malformation (shunts), cerebral aneurysm, spinal cord compression (from disease), carcinomatous meningitis, or stroke. All subjects should undergo a CT scan or MRI of the brain.
- a. Transient ischemic attack >1 month prior to screening is allowed.
 - b. 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 PD) for at least 28 days by repeat imaging.
- Note: The repeat imaging 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).
6. Has a current malignancy other than inclusion diagnosis, except for:
- a. Cervical carcinoma of Stage 1B or less.
 - b. Noninvasive basal cell or squamous cell skin carcinoma.
 - c. Noninvasive, superficial bladder cancer.
 - d. Prostate cancer with a current PSA level < 0.1 ng/mL.

- e. Any past malignancy considered cured for ≥ 2 years (ie, eligible subjects must have complete response of ≥ 2 years duration).
- 7. Has known allergies, hypersensitivity, or intolerance to trial treatment or its excipients as well as known or suspected allergy or intolerance to any agent given in the course of this trial.
- 8. Has contraindications to the use of pembrolizumab, pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, cisplatin or carboplatin per local prescribing information as applicable for the planned trial treatment.
- 9. Is a female who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this trial or within 6 months after the last dose of trial treatment or intends to conceive children within 6 months of ending trial treatment.
- 10. Is a male who plans to father a child while enrolled in this trial or within 6 months after the last dose of trial treatment.
- 11. 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. Additionally, vulnerable subjects or subjects under guardianship, curatorship, judicial protection or deprived of liberty, are excluded from participation in this trial.
France: See Section 10.10.3 for requirements per local health authorities.
- 12. Has a known history of seropositivity for HIV. *Note: HIV testing is required at screening only if required per local health authorities or institutional standards.*
- 13. Hepatitis (testing for hepatitis B or C is not required unless mandated by local health authority):
 - a. HBV: Has a medical history or positive serology for HBV (defined as positive for HBsAg or HBV DNA).
 - Above is not exclusionary if deemed due to vaccination, resolved natural infection, or passive immunization due to immunoglobulin therapy.
 - b. HCV: Known active HCV infection (defined as positive for HCV RNA [qualitative]).
- 14. Substance abuse or medical, psychological, or social conditions that may interfere with the subject's participation in the trial or evaluation of the trial result.
- 15. Has been dosed before in this trial.
- 16. 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 (in the dose escalation only if outside of the DLT observation period.).*

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 Sections 5.1 and 5.2) as assessed during screening. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to follow ICH guidelines, meet the CONSORT publishing requirements, and to respond to queries from regulatory authorities. Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, subject withdrew consent, or other reasons), and any AEs related to a protocol-mandated procedure (eg, tumor biopsy, CT scan), including washout or discontinuation of prior medications. Rescreening is not allowed.

6 TRIAL TREATMENT

6.1 Investigational and Auxiliary Medicinal Products

Trial treatment is defined as any IMP, AMP, or medical device(s) intended to be administered to a trial subject according to the trial protocol. IMP(s) specifically are referred to as trial drug(s).

In the dose escalation phases 1a or 1b, subjects will be administered GEN1055 according to DLs outlined in Section 4.1.1 and 4.1.2.

Trial treatment should be administered as described in Table 6-1, Table 6-2 and Table 6-3 until 1 or more of the discontinuation criteria in Section 7 are met. For combination therapy regimens, the gap between drugs can range from CCI [REDACTED] for subjects' convenience (meal breaks, short walks, managing IRRs, etc.) as long as the start times of every component of combination regimens are duly recorded.

As a routine precaution, all subjects must be observed during Cycle 1 and Cycle 2 on Day 1 for at least 4-6 hours after ending infusion of the last trial treatment. For all subsequent cycles, subjects must be observed for at least 2 hours after ending infusion of the last trial treatment, unless they have experienced an IRR in any previous cycle. In the latter case, the clinical observation should continue to be 4-6 hours.

Detailed dose modification guidance is provided in Section 6.8. Information regarding concomitant therapy is provided in Section 6.7.

Table 6-1 Investigational Medicinal Product(s)

Trial Drug Name	GEN1055 ^{a,b}	Pembrolizumab ^{a,b} (Phase 1b and EC1 ^c)
Dosage Formulation	Concentrate for solution for infusion	
Dose (including schedule and cycle length)	Phase 1a/1b: - CCI (interim DLs to be considered; see Sections 4.1.1 and 4.1.2), Q3W (21-day cycles) Phase 2a: - expansion dose(s), Q3W (21-day cycles)	Phase 1b: 200 mg, Q3W (21-day cycles) Phase 2a, EC1 ^c only: 200 mg Q3W (21-day cycles) For pembrolizumab containing regimens, treatment should not exceed 24 months.
Route of Administration	IV (≥60 minutes)	IV (30 minutes)
Dosing Instructions	Refer to the IMP Manual for additional details.	According to locally approved label
Hospitalization/ Monitoring Guidance	During dose escalation, an overnight stay will be required for the first subject in each DL and may be required for additional subjects if recommended by the sponsor.	
Packaging	CCI	Glass vial containing 4 mL (25 mg/mL).
Labeling	Trial drug label will contain information to meet the applicable regulatory requirements. For further details see the IMP Manuals.	

DL=dose level; EC=expansion cohort; IMP=investigational medicinal product; IV=intravenous(ly); Q3W=every 3 weeks; PD=progressive disease.

- Refer to the IMP Manual for further details.
- Refer to Section 10.10.1 for EU authorization status.
- Only for subjects receiving GEN1055+pembrolizumab following PD on GEN1055 monotherapy.

Infusion times and recommendations may be adjusted by the sponsor in consultation with investigators, based on emerging safety information. Infusion durations that exceed the planned length of time due to IV bag overfill, minor equipment calibration factors, and/or subject factors not under the control of administering personnel will not be considered protocol deviations. The actual infusion time should be accurately documented.

Table 6-2 Auxiliary Medicinal Product(s)

AMP Name	Pembrolizumab ^a (EC1, EC2, EC3, EC4 and EC5)	Pemetrexed ^a	Paclitaxel ^{a,b}	Nab-paclitaxel ^a	Gemcitabine ^a + carboplatin ^a	Cisplatin ^a	Carboplatin ^a
Use	SoC	SoC	SoC	SoC	SoC	SoC	SoC
Dosage/ frequency	200 mg Q3W (Day 1)	EC3: 500 mg/m ² Q3W (Day 1)				EC3 (Option1) ^c : 75 mg/m ² Q3W (Day 1), only C1-C4	EC3 (Option 2) ^c : AUC 5 Q3W (Day 1), only C1-C4
			EC4 (Option 1) ^d : 200 mg/m ² Q3W (Day 1), only C1- C4	EC4 (Option 2) ^d : 100 mg/m ² on Days 1, 8 and 15 of each Q3W cycle, only C1- C4			EC4: AUC 6 Q3W, (Day 1) only C1-C4
			EC5 (Option 1) ^e : 90 mg/m ² (Days 1, 8 and 15 of each Q4W cycle	EC5 (Option 2) ^e : 100 mg/m ² on Days 1, 8 and 15 of each Q4W cycle	EC5 (Option 3) ^e : Gemcitabine 1000 mg/m ² and Carboplatin AUC 2 mg/mL/min on Days 1 and 8 of each Q3W cycle		
Route of Administration	IV	IV	IV	IV	IV	IV	IV (per local practice)
Dosing Instructions	According to locally approved label and Section 6.7.4.						
Labeling	AMP labels will contain information to meet the applicable regulatory requirements.						

AMP=auxiliary medicinal product; AUC=area under the concentration-time curve (in mg×mL/min); min=minutes; C=cycle; EC=expansion cohort; IV=intravenous(ly); min=minutes; SoC=standard of care; Q3W=every 3 weeks; Q4W=every 4 weeks.

- Refer to Section 10.10.1 for EU authorization status. For unauthorized AMPs, refer to Section 6.4.2 for details regarding drug accountability and destruction.
- Paclitaxel should be completely administered before initiating the carboplatin dose.
- In EC3, either cisplatin **or** carboplatin at the investigator's discretion.
- In EC4, either paclitaxel **or** nab-paclitaxel at the investigator's discretion.
- In EC5, either paclitaxel **or** nab-paclitaxel **or** gemcitabine+carboplatin at the investigator's discretion.

In the expansion phase 2a, subjects will be administered the expansion dose(s) from dose escalation phase 1a or 1b for either GEN1055 monotherapy or combination therapy, respectively. A proposed treatment sequence overview for the expansion part is provided in [Table 6-3](#).

Table 6-3 Expansion - Proposed Trial Treatment Sequence Overview

Expansion Cohort	Pembrolizumab	GEN1055	Pemetrexed	Paclitaxel/ nab-paclitaxel ^a	Paclitaxel/ nab-paclitaxel/ gemcitabine+ carboplatin ^b	Cisplatin/ carboplatin ^c	Carboplatin
CCI [REDACTED] ^d		1					
CCI [REDACTED]	1	2					
CCI [REDACTED]	1	2	3			4 ^e	
CCI [REDACTED]	1	2		3 ^e			4 ^e
CCI [REDACTED]	1	2			3		

CCI [REDACTED]

Numbers represent treatment sequence if to be administered on the same day (see [Table 6-1](#) and [Table 6-2](#)).

- a. Paclitaxel or nab-paclitaxel at investigator's discretion.
- b. Paclitaxel or nab-paclitaxel or gemcitabine+carboplatin at investigator's discretion.
- c. Cisplatin or carboplatin at investigator's discretion.
- d. If subjects are to receive GEN1055+pembrolizumab following PD on GEN1055 monotherapy, pembrolizumab should be administered first.
- e. Only for the first 4 treatment cycles.

6.2 Dosage and Administration

6.2.1 GEN1055

GEN1055 will be administered using IV infusion (≥ 60 min) Q3W on Day 1 after all procedures and assessments have been completed.

In the dose escalation part, subjects will be administered GEN1055 according to dose levels outlined in Sections 4.1.1 and 4.1.2.

In the expansion part, subjects will be administered dose regimen(s) of GEN1055 as determined by the results in the dose escalation part (phase 1a and 1b), as follows:

- In EC1, subject will receive GEN1055 monotherapy.

Note: In case of PD on GEN1055 monotherapy (EC1), subjects may have the option to receive combination therapy with GEN1055+pembrolizumab by following EC2 activities.

- In EC2, subjects will receive GEN1055 in combination with pembrolizumab.
- In EC3, subjects will receive 4 cycles of GEN1055 in combination with pembrolizumab, pemetrexed, and cisplatin **OR** carboplatin followed by GEN1055 in combination with pembrolizumab and pemetrexed as maintenance therapy.
- In EC4, subjects will receive 4 cycles of GEN1055 in combination with pembrolizumab, carboplatin, and paclitaxel **OR** nab-paclitaxel followed by GEN1055 in combination with pembrolizumab as maintenance therapy.
- In EC5, subjects will receive GEN1055 in combination with pembrolizumab and paclitaxel **OR** nab-paclitaxel **OR** gemcitabine+carboplatin.

For combination therapies, the sequence of administration of each therapy is detailed in Table 6-3. The gap between drugs can range from CCI [REDACTED] for subjects' convenience (meal breaks, short walks, managing IRRs, etc) as long as the start times of every component of combination regimens are duly recorded.

Please refer to the IMP Manual for additional information regarding GEN1055 administration.

6.2.2 Pembrolizumab

In phase 1a and 1b, EC1 (if applicable; see Section 6.2.1), EC2, EC3, EC4 and EC5, pembrolizumab 200 mg will be administered Q3W on Day 1, after all pretreatment procedures and assessments have been completed. Pembrolizumab is administered as an IV infusion over 30 minutes. Combination therapy regimens and sequences are detailed in Section 6.1 and 6.2.1. Pembrolizumab must be promptly followed by a saline flush to clear the line before starting the infusion of GEN1055. Dose modifications (increase or decrease) of pembrolizumab are not allowed.

6.2.3 Pemetrexed

Pemetrexed will be administered as an IV infusion over 10 minutes Q3W on Day 1 as per approved label. 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 6.7.4 for further details related to the potential impact on immunotherapy).

Pemetrexed will be prepared and administered as per the approved label, at the dose of 500 mg/m². The weight on D1 of each cycle should be used for surface area calculations. All subjects should receive the appropriate supplementation of Vitamin B12 and folic acid premedication given in accordance with approved product label and/or standard practice, and also should be documented as concomitant therapy preceding pemetrexed administration.

Combination therapy regimens and sequences are detailed in Section 6.1 and 6.2.1.

6.2.4 Paclitaxel

In EC4 (Option 1), paclitaxel 200 mg/m² will be administered as an IV infusion over 3 hours Q3W on Day 1 for 4 cycles as per the approved label. Administration of paclitaxel must be complete before initiating carboplatin. In EC5 (Option 1), paclitaxel 90 mg/m² will be administered as an IV infusion over 3 hours on Days 1, 8 and 15 of each Q4W cycle as per the approved label. The weight on D1 of each cycle should be used for surface area calculations. All subjects should be premedicated with oral or IV steroid and antihistamines according to the approved product label and/or standard practice (refer to Section 6.7.4 for further details related to the potential impact on immunotherapy). Additional premedications should be administered as per standard practice.

Combination therapy regimens and sequences are detailed in Section 6.1 and 6.2.1.

6.2.5 Nab-paclitaxel

In EC4 (Option 2), nab-paclitaxel will be administered on Days 1, 8, and 15 of each Q3W cycle for 4 cycles by IV infusion at a dose of 100 mg/m² over 30 to 40 minutes as per the approved label. Nab-paclitaxel should be completely administered before initiating the carboplatin dose. In EC5 (Option 2), nab-paclitaxel will be administered on Days 1, 8, and 15 of each Q4W cycle by IV infusion at a dose of 100 mg/m² over 30 to 40 minutes as per the approved label. The weight on D1 of each cycle should be used for surface area calculations.

Combination therapy regimens and sequences are detailed in Section 6.1 and 6.2.1.

6.2.6 Cisplatin/Carboplatin

Treatment of cisplatin or carboplatin will be prepared and administered as per the approved label.

In EC3 and EC4, cisplatin **OR** carboplatin will be administered on Day 1 of each Q3W cycle for 4 treatment cycles.

In EC5 (Option 3) carboplatin will be administered on Days 1 and 8 of each Q3W cycle.

Combination therapy regimens and sequences are detailed in Section 6.1 and 6.2.1.

Cisplatin dose

Cisplatin is administered as a dose of 75 mg/m² 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. The weight on D1 of each cycle should be used for surface area calculations. The body surface area in m² should be calculated per local guidance.

Carboplatin dose

Carboplatin will be administered using IV infusion at the protocol-specified dosages of either of the following:

- EC3 (Option 2): AUC 5 mg/mL/min on Day 1 of each Q3W cycle on Day 1 for 4 treatment cycles.
- EC 4: AUC 6 mg/mL/min on Day 1 of each Q3W cycle on Day 1 for 4 treatment cycles.
- EC5 (Option 3): AUC 2 mg/mL/min on Days 1 and 8 of each Q3W cycle

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 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 NCI-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 (refer to Section 6.7.4 for further details related to the potential impact on immunotherapy).

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 6.8.4 and Section 10.7).

6.2.7 *Gemcitabine*

In EC5 (Option 3), gemcitabine will be administered at a dose of 1000 mg/m² IV over 30 minutes in combination with carboplatin AUC 2 mg/mL/min on Days 1 and 8 of each 21-day cycle (see current KEYTRUDA prescribing information for more details).

Combination therapy regimens and sequences are detailed in Section 6.1 and 6.2.1.

6.3 Product Complaints

A product 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 complaint may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of 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 complaint information; all trials conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Product complaints must be reported to the sponsor's QA department by trial-site personnel, within 24 hours of awareness of the event. The IMP Manual contains contact information (email and telephone) for Genmab QA and instructions for reporting complaints.

In addition to reporting the complaint, if the product defect is combined with an AE or SAE, the trial-site personnel must report the AE or SAE to the sponsor according to the AE and SAE reporting process and timelines (refer to Section 8.4). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.4 Preparation/Handling/Storage/Accountability

6.4.1 Preparation, Handling, and Storage

Guidance for the preparation, handling, and storage of trial treatment is described in the IMP Manual.

6.4.2 Drug Accountability and Destruction

The investigator or designee must maintain an accurate record of received, returned, and/or destroyed trial treatment and administration of trial treatment to trial subjects in a drug accountability log/record. Drug accountability will be verified by the site monitor on a continuous basis and at the completion of the trial.

When drug accountability has been verified by the site monitor, all expired/unused trial treatment (eg, vials, capsules, prefilled syringes) can be destroyed or returned to the sponsor in accordance with the guidance in the IMP Manual.

Final drug accountability will be assessed at the end of the trial (or at site closure, if applicable) in accordance with local regulations and guidelines.

6.5 Measures to Minimize Bias: Randomization and Blinding

This is an open-label trial; therefore, blinding of treatment will not be performed.

If more than 1 GEN1055 dose regimen is chosen for any of the phase 2a ECs based on data from phases 1a or 1b, symmetrical randomization within each EC will be used to avoid bias in the assignment of subjects to treatment dose regimen groups, with potential stratification in some ECs. Randomization will occur centrally using an IRT system.

6.6 Compliance

The trial treatment will be administered in the controlled environment of a clinical research center, and the direct observation of trial treatment administration by trial staff will ensure

compliance with trial requirements. The date and time of each trial treatment administration will be documented.

Treatment start and stop dates, including dates for trial treatment delays and/or dose reductions will also be documented.

6.7 Prior and Concomitant Therapies

The sponsor's medical officer (or delegate) should be contacted if there are any questions regarding prior or concomitant medication or therapies.

6.7.1 Prior Anticancer Therapies

Prior anticancer therapies received from the time of initial diagnosis and until the first dose of trial treatment for the treatment of malignant solid tumors (including surgery, RT, chemo-radiotherapy, systemic treatment regimens etc) must be documented.

The best response, reason for discontinuation, dates of administration, and date of progression should be reported for prior anticancer therapies.

Refer to Section 5.2 and 6.7.3.2 for details regarding prohibited prior anticancer therapies or washout periods for prior anticancer therapies.

6.7.2 Other Prior Therapies

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) received within 28 days before administration of the first dose of trial treatment must be documented.

Refer to Section 5.2 and 6.7.3.2 for details regarding prohibited prior therapies or washout periods for prior therapies.

6.7.3 Concomitant Therapies

The subject must be told to notify the trial site about any new medications (including over-the-counter or prescription medicines, vitamins, and vaccines) they take after the start of the trial treatment. All medications (other than the trial treatment) and significant nondrug therapies (including physical therapy, herbal/natural medications, and blood transfusions) administered during the trial (ie, beginning with administration of the first dose of trial treatment until 90 days after the last dose of trial treatment) must be documented. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be documented.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" (Section 6.7.3.2).

Concomitant therapies should also be documented beyond 90 days only in conjunction with worsening AEs or new SAEs related to trial treatment.

6.7.3.1 *Permitted Concomitant Therapies*

The following concomitant medication and therapies are permitted during the trial, and should be documented.

- SARS-CoV-2 vaccine is generally permitted, including mRNA-based, protein-based, or nonreplicating viral vector-based vaccines. Consider choosing an appropriate type of SARS-CoV-2 vaccine and consult with an infectious disease expert if desired. SARS-CoV-2 vaccine should not be administered during the DLT observation period.
- Palliative RT during the trial will be allowed for local pain control provided that:
 - (i) in the opinion of the investigator, 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.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia and $\geq$ grade 3 neutropenia, when clinically indicated or at the investigator's discretion. In case of recurring $\geq$ grade 3 neutropenia, use of growth factors is mandated.
- Red blood cell and platelet transfusions, if clinically indicated.
- Steroid treatment is permitted to modulate symptoms of an irAE at the discretion of the investigator (refer to Section 6.8). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is also allowed.
- Multivitamins, vitamin D, calcium, and supplements, for prevention of weight loss.
- Prescribed medicinal cannabinoids as palliative therapy.

The trial site will supply supportive medication, eg, pre-infusion medication, post-infusion medication, antiviral medication.

6.7.3.2 *Prohibited Concomitant Therapy*

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

The following concomitant therapies are prohibited from during trial treatment:

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

- Immunosuppressive doses of systemic corticosteroids (ie, prednisone >10 mg daily) for any purpose other than to modulate AEs of suspected immunologic etiology are prohibited with the following exception: subjects are permitted the use of topical, ocular, intraarticular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Short-term oral or IV use in doses >10 mg/day prednisone equivalent for chronic obstructive pulmonary disease exacerbations OR adrenal replacement steroid doses >10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of nonautoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) up to a cumulative dose of 200 mg prednisone is permitted.
- Live or live attenuated vaccines within 28 days prior to the first dose of trial treatment, while participating in the trial, and for 3 months following the last dose of trial treatment administration.
Note: Seasonal influenza vaccines are generally killed virus vaccines and are permitted; however, intranasal influenza vaccines are live attenuated and are not allowed.
- Escalation phase 1a and 1b: Administration of SARS-CoV-2 vaccine during the DLT period.

Treatment with bisphosphonates (eg, pamidronate, zoledronic acid, etc) and RANK-L inhibitors initiated within 28 days before the first planned dose of trial treatment administration or planned to be initiated during the first 4 weeks of trial treatment, unless approved by sponsor.

Information on potential drug-drug interactions is unknown for GEN1055. Caution should be used regarding the use of herbal medications as there may be unknown interactions with trial treatment(s). Discontinuation of the use of herbal medications prior to trial enrollment is encouraged.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

6.7.4 Premedication and Antiemetics for Subjects Receiving Combination Therapy

Premedication for SoC should be given according to the locally approved label and/or standard practice for each AMP (Section 6.2 and Table 6-2). Any such premedication should be recorded as concomitant medication.

As supplemental guidance, 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 GEN1055 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.

All subjects treated with paclitaxel should be premedicated with steroid and antihistamines according to the approved product label and/or standard practice.

All subjects treated with pemetrexed should be premedicated with folic acid and Vitamin B12 according to the approved product label and/or standard practice and dexamethasone is also recommended.

6.8 Dose Modification and Stopping Rules

6.8.1 Dose-Limiting Toxicity

The DLT evaluation period is defined as 21 days from the first dose of trial drug. Subjects who do not experience a DLT during Cycle 1 (the first 21 days of dosing) will be considered to have sufficient safety evaluations and DLT evaluable if they have been observed for ≥ 21 days following the first dose and are considered by both the sponsor and investigators to have enough safety data to conclude that a DLT did not occur. Toxicities will be graded for severity according to the NCI-CTCAE, v5.0. CRS and ICANS will be evaluated according to the ASTCT criteria ([Lee et al., 2019](#)).

The occurrence of any of the toxicities outlined in this section will be considered a DLT if occurring within the DLT evaluation period, unless clearly related to underlying disease or extraneous causes.

- All grade 5 events
- Anaphylaxis
- Grade ≥ 3 IRR
- Hematological events listed below:
 - Grade 4 neutropenia (ie, ANC $< 0.5 \times 10^9$ cells/L [$< 500/\mu\text{L}$]) lasting more than 7 days
 - Grade 4 thrombocytopenia (platelet count $\leq 25.0 \times 10^9$ platelets/L [$< 25,000/\mu\text{L}$]) for ≥ 7 consecutive days
 - Grade 3 and grade 4 febrile neutropenia (neutrophil count $< 1.0 \times 10^9$ cells/L with a single temperature of $> 38.3^\circ\text{C}$ [100.9°F] or with a sustained temperature of $\geq 38^\circ\text{C}$ [$\geq 100.4^\circ\text{F}$] for more than 1 hour)
 - Grade 3 and grade 4 hemorrhage associated with thrombocytopenia of $\geq$ grade 3 requiring platelet transfusion.
 - Grade 4 anemia
- Nonhematological events listed below:
 - AST or ALT elevations $\geq$ grade 2 with concomitant bilirubin $> 2.0 \times \text{ULN}$ with no signs of cholestasis and no other reason can be found to explain the combination of increased ALT/AST and total bilirubin, ie, a Hy's law case

- All nonhematological toxicities of grade ≥ 3 (severe or life-threatening), **excluding** the following:
 - Grade 3 fever (>40.0 °C [>104.0 °F]) for ≤ 24 hours
 - Grade 3 hypotension (medical intervention indicated; hospitalization indicated) resolving in ≤ 24 hours
 - Grade 3 anorexia when grade 2 anorexia was present at baseline or that lasts for <14 days after the last IMP administration
 - Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
 - Grade 3 fatigue for less than 7 days
 - Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
 - Grade ≥ 3 amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a DLT

The investigator must notify the medical officer (or delegate) immediately of a DLT. Frequent laboratory monitoring of CBC including differential should be initiated to document start and resolution of hematological AEs. All AEs occurring during the defined DLT evaluation period will be assessed according to the criteria above. All treatment-related AEs will be monitored and included in the evaluation of the toxicity profile of trial treatment unless the event is clearly determined to be unrelated to trial treatment (eg, disease progression).

Subjects experiencing a DLT within the DLT evaluation period should discontinue trial treatment immediately. If requested by the investigator, the sponsor may allow a subject with a DLT to continue in the trial. For this decision, a thorough benefit/risk assessment of the individual subject is required.

If a subject experiences a toxicity that would have qualified as a DLT, but occurs after the DLT evaluation period, the subject's benefit/risk must be thoroughly assessed. Continued treatment with trial treatment must be agreed between the sponsor and the investigator.

For subjects who receive treatment beyond the DLT evaluation period, all corresponding AEs that would have met the DLT criteria will be considered for the purpose of determining the expansion dose(s) and/or MTD (if reached). For the declaration of the expansion dose(s) from the dose escalation part for further development of GEN1055 in the expansion, the totality of the data including safety, PK, pharmacodynamics, and preliminary efficacy will be evaluated.

6.8.2 Dose Modification Guidance and Stopping Criteria for GEN1055 and Pembrolizumab

6.8.2.1 Dose Reductions for GEN1055 and Pembrolizumab

No dose modification (increase or decrease) of GEN1055 or pembrolizumab will be permitted for this trial.

6.8.2.2 Dose Delays and Interruptions for GEN1055 and Pembrolizumab

For information on trial treatment safety stopping rules, see Section 6.8.5.

The doses of GEN1055 or pembrolizumab cannot be reduced but may be delayed.

- Administration of GEN1055 or pembrolizumab can be delayed for up to 21 days (ie, 1 cycle) unless otherwise approved by the sponsor's medical officer. If the severity of a treatment-related AE resolves to $\leq$ grade 1 or baseline within this period, retreatment may be considered under the following conditions:
 - In case of safety concerns, and for subjects who experience a recurrence of the same AEs of $<$ grade 3 severity with rechallenge of trial treatment, a consultation between the sponsor and investigator will occur to determine whether the subject should continue trial treatment at the same schedule or whether the dosing interval in subsequent cycles should be increased.
 - A subject who experiences the same AE of $\geq$ grade 3 with rechallenge of trial treatment must discontinue treatment immediately, as follows:
 - If the AE occurred after pembrolizumab infusion, but before GEN1055 infusion: both GEN1055 and pembrolizumab must be discontinued.
 - If the AE occurred after GEN1055 infusion, GEN1055 must be discontinued. The subject may only continue pembrolizumab $\pm$ chemotherapy at the discretion of the investigator, if deemed that the benefit/risk balance for doing so is favorable.

Further details on treatment discontinuation are provided in Section 7.1.

Decisions regarding dosing modification of trial treatment should be made using clinical judgment, considering relatedness of the AE to the trial treatment and the subject's underlying condition. For guidance, please see Table 6-4. The investigators are encouraged to contact the sponsor in case of any safety concern that needs thorough discussion and evaluation.

Note that specific rules apply for irAEs, thrombocytopenia, neutropenia, CRS, ICANS and IRRs (see Sections 6.8.2.3 and 6.8.3).

Table 6-4 Dosing Modification and Management of Treatment-Related AEs

NCI-CTCAE Grade/Severity	Hold Treatment (Y/N)	Dosing Modification
Grade 1 or Grade 2 (Mild or moderate)	N	Continue treatment at the discretion of the investigator.
Grade 3 (Severe)	Y	Withhold treatment until resolution to $\leq$ grade 1 or baseline.
Grade 4 (Life-Threatening)	Y	Permanent discontinuation except if approved by the sponsor's medical officer. If continuing on treatment, toxicity must resolve to grade 1 or baseline.

AE=adverse event; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; N=no; Y=yes.

For recurrent treatment-related AEs upon rechallenge, please see guidance in text.

6.8.2.3 Toxicity Management for Immune-Related AEs for GEN1055 and Pembrolizumab

AEs associated with GEN1055 or GEN1055+pembrolizumab may represent an irAE. 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 (Schneider et al., 2021). Guidance for dose modification and management of irAEs is provided in Table 6-5. 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 Guideline Update* (Schneider et al., 2021).

General Guidance

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, trial treatment should be withheld or permanently discontinued, and corticosteroids administered.
- For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids (also see Table 6-5).
- Corticosteroid tapering should be initiated upon AE improving to grade 1 or less — continue to taper over at least 4 weeks.
- Trial treatment may be resumed after the AE has resolved to $\leq$ grade 1.
Note: The corticosteroid dose must be ≤ 10 mg/day before treatment is resumed.
- For grade 1 irAEs, trial treatment should be continued with close monitoring unless otherwise noted in Table 6-5.

- For > grade 1 irAEs, withhold treatment until resolution to ≤ grade 1 unless otherwise specified in [Table 6-5](#).
- Permanent discontinuation of trial treatment is recommended for grade 4 toxicities with the exception of endocrinopathies that have been controlled by hormone replacement.
- Trial treatment should also be permanently discontinued for any serious grade 3 irAE that recurs and for any life-threatening irAE. Also consider permanently discontinuing trial treatment for grade 3 AST, ALT, or bilirubin increases (see [Table 6-5](#) for details).

Table 6-5 Dosing Modification and Management of Immune-Related Adverse Events

Immune-Related AEs	Toxicity Grade (NCI-CTCAE v5.0)	Dose Modification	Guidance for Management of irAEs
Pneumonitis	Grade 1	<u>Withhold treatment or proceed with close monitoring</u>	• 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. Consider bronchoscopy with BAL ± transbronchial biopsy. Add prophylactic antibiotics for opportunistic infections. • For ≥ grade 3: Administer methylprednisolone IV 1 to 2 mg/kg.
	Grade 2	<u>Withhold treatment until</u> resolution to ≤ grade 1 and corticosteroid has been tapered ^a	
	Grade 3 or Grade 4	Permanently discontinue	
Colitis	Grade 2	Withhold treatment until resolution to ≤ grade 1 and corticosteroid has been tapered ^a	• Monitor for signs and symptoms of colitis. Consider gastroenterology consultation and confirm diagnosis of colitis. Endoscopic evaluation for cases grade 2 or higher. • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Consider adding infliximab or vedolizumab if inadequate response. • Grade 4: Administer 1 to 2 mg/kg methylprednisolone IV or equivalent followed by taper.
	Grade 3	Withhold treatment until resolution to ≤ grade 1 and corticosteroid has been tapered ^a	
	Grade 4	Permanently discontinue	
Hepatitis (ALT, AST, or bilirubin increased)	Grade 2 (asymptomatic)	Withhold treatment until resolution to ≤ grade 1 and corticosteroid has been tapered ^a	• Initiate work-up for other causes of elevated liver enzymes such as viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, and cross-sectional imaging for potential liver metastasis. • Liver function tests must be monitored closely, the first time within 48 hours, and at least twice per week (unscheduled visits) for up to 4 weeks until resolution to ≤ grade 1. • Consider immediate administration of corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) or at the latest within 3 days if no improvement, followed by taper.

Immune-Related AEs	Toxicity Grade (NCI-CTCAE v5.0)	Dose Modification	Guidance for Management of irAEs
			For AST or ALT elevations $\geq$ grade 2 with concomitant bilirubin $>2.0 \times$ ULN with no signs of cholestasis, ie, a Hy's law case, permanently discontinue.
	Grade 3 or symptomatic	Permanently discontinue if symptomatic If asymptomatic withhold treatment until resolution to $\leq$ grade 1 and corticosteroid has been tapered - If the grade 3 AST, ALT, or bilirubin increase resolves to $\leq$ grade 1 within 14 days, IMP may be continued after sponsor medical monitor approval - If the grade 3 AST, ALT, or bilirubin increase does NOT resolve to $\leq$ grade 1 within 14 days, permanently discontinue IMP	- Initiate work-up for other causes of elevated liver enzymes such as viral hepatitis, alcohol history, iron study, thromboembolic event, liver ultrasound, and cross-sectional imaging for potential liver metastasis. - Monitor liver function tests (unscheduled visits) twice per week for up to 4 weeks until resolution to $\leq$ grade 1. - Immediately administer corticosteroids (grade 3: initial dose of 1-2 mg/kg methylprednisolone IV or equivalent; Grade 4: 2 mg/kg methylprednisolone IV or equivalent) followed by taper. - Consider adding prophylactic antibiotics for opportunistic infections. - If no improvement within 3-5 days despite methylprednisolone IV or equivalent is observed, consider prompt treatment with immunosuppressive therapy (eg, mycophenolate mofetil at 500 mg every 12 hours; discuss with medical monitor). <u>Infliximab should not be used.</u> - Hepatology consult, abdominal workup, and imaging as appropriate.
	Grade 4	Permanently discontinue	
T1DM or Hyperglycemia	Newly diagnosed T1DM or Grade 3-Grade 4 hyperglycemia	Withhold until glucose control is obtained ^{b,c}	- Monitor for hyperglycemia or other signs and symptoms of diabetes. Consider endocrine consultation. - Consider administration of insulin for type 1 diabetes. - Consider administration of antihyperglycemic agents in subjects with hyperglycemia.
Hypophysitis	Grade 2	Continue treatment at the discretion of the investigator	- Monitor for signs and symptoms of hypophysitis. Consider endocrine 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 ^b	
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	
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 ^{b,c}	
Nephritis and renal dysfunction	Grade 1	Consider temporary hold pending consideration of baseline renal function and to confirm etiology ^a	Monitor subjects for elevated or changes in serum creatinine before every dose.
	Grade 2	Withhold treatment until resolved to baseline ^a	

Immune-Related AEs	Toxicity Grade (NCI-CTCAE v5.0)	Dose Modification	Guidance for Management of irAEs
	Grade 3-Grade 4	Permanently discontinue	For $\geq$ grade 2: If worsening or no improvement, consider administration of corticosteroids (prednisone 0.5 to 2 mg/kg or equivalent) followed by taper. Corticosteroid taper should be initiated upon irAE improving to grade 1 or less. Consider nephrology consultation.
Cutaneous 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. Monitor closely for improvement regardless of grade. If SJS or TEN is confirmed, permanently discontinue.
	Grade 3	Withhold treatment until resolved to $\leq$ grade 1 ^a	
	Grade 4	Permanently discontinue	
For other ^d	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 ^b	

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BAL=bronchoalveolar lavage; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; DEC=Dose Escalation Committee; IMP=investigational medicinal product; irAE=immune-related adverse event; IV=intravenous(ly); SJS=Stevens-Johnson syndrome; T1DM=type 1 diabetes mellitus; TEN=toxic epidermal necrolysis; TSH: thyroid-stimulating hormone; ULN=upper limit of normal.

a. The next dose of IMP can maximally be delayed 21 days unless otherwise approved by the sponsor's medical officer. If irAE resolves within 21 days to baseline, restart treatment at the same dose level after consulting the sponsor's medical officer.

b. Investigator must contact the sponsor to discuss whether the subject should be withdrawn from IMP treatment or if the next dose should be delayed. Subjects may be treated with the same dose and schedule. The sponsor may also consult the DEC as specified in Section 10.1.8.

c. For subjects with grade 3 or 4 immune-related endocrinopathy leading to withholding of IMP dosing, treatment may be resumed when the AE recovers to $\leq$ grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

d. Refer to (Schneider et al., 2021) for guidance on immune-related musculoskeletal, nervous system, hematologic, cardiovascular, ocular and specific cutaneous toxicities.

Attribution of Toxicity

When GEN1055 is administered in combination with pembrolizumab (GEN1055+pembrolizumab $\pm$ chemotherapy), attribution of an AE to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to GEN1055, pembrolizumab or both for AEs listed in Table 6-5, both treatment with GEN1055 and pembrolizumab must be withheld according to the recommended dosing modifications in Section 6.8.2.2. The subject may only continue chemotherapy at the discretion of the investigator, if deemed that the benefit/risk balance for doing so is favorable.

If the toxicities do resolve and conditions are aligned with what is defined in Table 6-5, GEN1055+pembrolizumab combination therapy may be restarted at the discretion of the investigator, even if chemotherapy is delayed. Reinitiation of GEN1055 as monotherapy may only be considered after communication with and approval by the sponsor. Re-initiation of pembrolizumab $\pm$ chemotherapy treatment may be considered at the discretion of the investigator, if it is deemed that the benefit/risk balance for doing so is favorable.

6.8.3 *Dosing Modification for Specific Adverse Events for GEN1055 and Pembrolizumab*

Dose modification guidance for specific AEs for GEN1055 and pembrolizumab are provided in the following sections as supplement to the local label for pembrolizumab.

For chemotherapy, please refer to Sections 6.8.4 and 10.9.

6.8.3.1 *Neutropenia and Febrile Neutropenia Associated With GEN1055 and Pembrolizumab Administration*

Table 6-6 Dosing Modification and Management of Neutropenia and Febrile Neutropenia

NCI-CTCAE Term	Toxicity Grade (NCI-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.

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

6.8.3.2 *Cytokine Release Syndrome Immune Effector Cell-Associated Neurotoxicity Syndrome Related to GEN1055 and Pembrolizumab*

In the unexpected case an event of CRS or ICANS occurs, grading of the CRS or ICANS should be made according to the ASTCT criteria ([Lee et al., 2019](#)).

Trial treatment should be permanently discontinued in case of a grade 4 CRS or ICANS event or a cytokine blockade-refractory grade 3 CRS or ICANS lasting >72 hours. However, per protocol, observation procedures and assessments are to continue until the subject withdraws from the trial or starts another course of systemic anticancer therapy.

Rescue medication, in terms of antidotes to reverse the action of GEN1055, are not available and potential events of CRS or ICANS must be treated symptomatically. Subjects with CRS or ICANS should receive supportive care following an international guideline ([Lee et al., 2014](#)) or local SoC, with supportive treatment controlling fever, hypotension, and hypoxia and in more severe cases with IL-6 mAb (tocilizumab), systemic steroids and vasopressors.

6.8.3.3 *Infusion-Related Reactions Associated With GEN1055 Administration*

As mitigation steps to prevent the occurrence of IRRs, the following recommendations and guidelines are provided:

- Premedication to prevent IRRs should be administered prior to each dose of GEN1055. As a minimum, premedication should include diphenhydramine at 50 mg (or an equivalent antihistamine) and acetaminophen/paracetamol at 1 g.

- Grade 1: If an IRR grade 1 occurs despite premedication with an antihistamine and acetaminophen/paracetamol, 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.
- Grades 2 to 3: If an IRR grade 2 or 3 occurs despite premedication with an antihistamine and acetaminophen/paracetamol, the infusion should be interrupted, and appropriate medical management instituted. The infusion may be restarted at the investigator's discretion at half the infusion rate under close medical supervision if symptoms have resolved to $\leq$ grade 1 within an hour and once the subject has received premedication that includes corticosteroids at a suggested maximum dose of 100 mg prednisone or equivalent. For subsequent use of corticosteroids, please consult the sponsor's medical officer.
 - If the subject has a second grade 3 IRR despite premedication, the infusion should be stopped, and the subject should discontinue trial treatment.
- Grade 4: If anaphylaxis or grade 4 IRR occurs, trial treatment should be discontinued immediately and permanently, and appropriate medical therapy should be administered.

Note:

- As a routine precaution, all subjects must be observed during Cycle 1 and Cycle 2 on Day 1 for at least 4-6 hours after ending infusion of the last trial treatment. For all subsequent cycles, subjects must be observed for at least 2 hours after ending infusion of the last trial treatment, unless they have experienced an IRR in any previous cycle. In the latter case, the clinical observation should continue to be 4-6 hours.
- During dose escalation, an overnight stay will be required for the first subject in each DL and may be required for additional subjects if recommended by the sponsor.
- Subjects must be observed in an area with resuscitation equipment and emergency agents.
- At all times during infusion of trial treatment, 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 premedications must be documented as concomitant medications.

6.8.3.4 *Infusion-Related Reactions Associated With 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.

6.8.4 Dose Modification for Chemotherapy

For pemetrexed, paclitaxel, nab-paclitaxel, gemcitabine, cisplatin and carboplatin, investigators should follow the local prescribing information or SoC for dose modifications and management of chemotherapy-related AEs. Supplemental guidance is provided in Section 10.7).

6.8.5 Safety Stopping Rules for Trial Treatment

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

- Subjects experiencing a DLT (refer to Section 6.8.1) should discontinue trial drug immediately. If requested by the investigator, the sponsor may allow a subject with a DLT to continue in the trial.
- If a subject experiences a toxicity that would have qualified as a DLT, but that occurs after the DLT evaluation period, the subject's benefit/risk must be thoroughly assessed. Continued treatment with GEN1055 and/or pembrolizumab must be agreed between the sponsor and the investigator.
- If the subject experiences a treatment-related AE that meets the criteria for treatment discontinuation as specified in Sections 6.8.2.3 and 6.8.3 and Table 6-5 and Table 6-6.
- An AE that fails to resolve to $\leq$ grade 1 within 21 days due to a toxicity possibly related to IMP, unless otherwise approved by the sponsor's medical officer.
- Treatment-related grade 4 or life-threatening AE, except with approval from the sponsor's medical officer.
- Second occurrence of an IRR of $\geq$ grade 3 despite premedication prior to the second infusion.
- First occurrence of anaphylaxis or a grade 4 IRR.
- Subjects with grade 4 transaminase or bilirubin elevation.
- Subjects with abnormal liver function parameters that meet Hy's law criteria as defined in Section 6.8.1.
- First episode of CRS or ICANS grade 4.
- First episode of cytokine blockade-refractory grade 3 CRS or ICANS lasting >72 hours.

Note:

- Subjects should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible for details regarding discontinuation of treatment (refer to Section 7.1).

6.8.6 *Safety Stopping Rules for the Trial*

The trial can/will be stopped for unacceptable toxicity as per Safety Committee recommendation and based on a risk-benefit assessment.

The expansion will be stopped if a 50% discontinuation rate due to AEs is observed at the time of the futility analysis (EC3 and EC4) or when 20 subjects have completed C1 (EC2 and EC5).

In addition, trial stopping rules for unacceptable toxicity will be introduced in the expansion part based on data collected during the dose escalation part of this trial.

6.9 Treatment of Overdose

6.9.1 *Overdose of GEN1055*

For this trial, an overdose of GEN1055 is defined as a subject receiving a dose in excess of 10% of that specified in this protocol.

Sponsor does not recommend specific treatment for an overdose.

In case of overdose, medication errors, misuse, and/or abuse of GEN1055, subjects should receive supportive care according to local guidelines and potential side effects of GEN1055 should be treated symptomatically.

In the event of an overdose, the investigator should:

- Contact the sponsor's medical officer (or delegate) immediately (see Section [8.4.3](#)).
- Closely monitor the subject for any AE/SAE and laboratory abnormalities.
- Consider plasmapheresis, in consultation with the sponsor.
- Obtain a serum sample for PK analysis if requested by the sponsor's medical officer (or delegate) (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.9.2 *Overdose of Pembrolizumab*

For this trial, 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.

6.9.3 *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.

6.9.4 *Overdose of Paclitaxel/Nab-paclitaxel*

There is no known antidote for paclitaxel or nab-paclitaxel overdose. 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.

6.9.5 *Overdose of Gemcitabine*

There is no known antidote for overdose of gemcitabine. Refer to the local prescribing information for more details.

6.9.6 *Overdose of Cisplatin*

There is no known antidote for cisplatin overdose. Acute overdose with cisplatin for injection may result in renal failure, hepatic failure, hearing loss, ocular toxicity, myelosuppression, nausea and vomiting, and neuritis. Management of overdose 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.

6.9.7 *Overdose of Carboplatin*

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

6.10 Continued Access to Trial Drug After the End of the Trial

For subjects with a potential treatment benefit, subjects may be eligible for continued treatment with Genmab IMP(s) by an extension protocol or as provided for by the local country's regulatory mechanism. However, Genmab reserves the unilateral right, at its sole discretion, to determine whether to supply Genmab IMP(s) and by what mechanism, after termination of the trial and before the product(s) is/are available commercially.

Refer to Section [10.10](#) for country-specific requirements.

7 DISCONTINUATION OF TREATMENT AND DISCONTINUATION FROM TRIAL

7.1 Discontinuation of Treatment

Subjects can decline to continue receiving trial treatment and/or other protocol-required therapies or procedures at any time during the trial but continue participation in the trial. Subjects who have discontinued trial treatment and/or other protocol-required therapies or procedures should not be automatically removed from the trial. Whenever safe and feasible, it is imperative that subjects remain on-trial to ensure safety surveillance and/or collection of outcome data (ie, continue efficacy evaluations according to the trial protocol).

The subject may discontinue both trial treatment and further participation in trial activities; however, they may continue to be followed for survival (see Section 7.1.3) and are not considered discontinued from the trial (see Section 7.2).

Reasons for discontinuation from trial treatment may include any of the following:

- Clinical progression
- Radiographic PD or confirmed radiographic PD by iRECIST (if applicable)
Note: If the investigator considers radiographic changes secondary to drug-induced inflammation and not to tumor progression, the investigator may postpone a diagnosis of PD until the next radiographic evaluation in the trial (see Section 8.2.4 for treatment beyond PD).
- Unacceptable AE(s) requiring treatment discontinuation (refer to Section 6.8).
- Subject request to discontinue trial treatment
- Sponsor or investigator decision
- Maximum treatment duration met
- Subject noncompliance
- Pregnancy of a trial subject
- Lost to follow-up
- Death
- Termination of the trial by the sponsor

For combination therapy: If a subject discontinues treatment with 1 or more IMP/AMPs as part of combination therapy, the subject can continue with the remaining components of the trial treatment at the discretion of the investigator, if the benefit/risk balance for doing so is considered favorable; and will be considered on-treatment. Subjects may only continue GEN1055 monotherapy if approved by the sponsor.

7.1.1 End of Treatment

The EoT visit should be conducted as soon as possible after the decision to end treatment. In addition, the subject will have a safety follow-up visit (see Section 7.1.2) and be followed for survival status through the end of the trial (see Section 7.1.3).

If the EoT visit coincides with a regularly scheduled cycle visit, the treatment discontinuation evaluations will supersede those of the regularly scheduled cycle visit. If the timing of the treatment discontinuation visit and first safety follow-up visit are the same, the treatment discontinuation visit may represent the first safety follow-up visit.

7.1.2 *Safety Follow-up Visit(s)*

Subjects discontinuing from treatment for any reason will have a safety follow-up visit 30 days (± 7 days; SFU1) and 90 days (± 7 days; SFU2) after the subject receives the last dose of trial treatment. If the subject initiates new anticancer treatment within 90 days of the last dose of trial treatment, the second safety follow-up visit should be performed prior to starting new anticancer treatment unless the first safety follow-up was completed < 30 days prior. The subject will move into survival status follow-up after the safety follow-up visit (see Section 7.1.3).

7.1.3 *Survival Status Follow-up*

Survival status will be assessed every 12 weeks (± 14 days), beginning from the day the subject receives the last trial treatment administration and continuing until the subject dies, withdraws consent for survival status follow-up, or the trial ends. Survival status may be requested more frequently around the time of a database lock or other trial milestones. Refer to Section 7.3 for guidance regarding subjects lost to follow-up.

Site personnel, or an independent third party, will attempt to collect the survival status of the subject within legal and ethical boundaries for all subjects enrolled. Survival status will be collected through medical records, national registries, or publicly available information as allowed per local regulation. If survival status is determined as deceased, this will be documented.

7.2 Discontinuation From the Trial

Reasons for discontinuation of a subject from the trial are:

- Death
- Lost to follow-up
- Sponsor decision
- Subject withdraws consent from trial participation
- Maximum trial duration met

If the reason for discontinuation from the trial is withdrawal of consent, then no additional assessments are allowed, but the sponsor may retain and continue to use any data collected before such a withdrawal of the consent. When a subject withdraws before completing the trial, the reason for withdrawal is to be documented, and the EoT visit assessments should be obtained whenever possible.

If a subject withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the investigator must notify the sponsor accordingly (see Section 10.4 for further details).

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site. The following actions must be taken if a subject fails to return to the clinic for a required trial visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the trial.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, the subject will be considered to have discontinued from the trial.

8 TRIAL ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of all assessments applicable to this trial.

All assessments should be performed prior to trial treatment administration, unless otherwise indicated in the Schedule of Activities. Collections for PK and biomarker assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual and trial samples flowchart that will be provided. Collection, handling, storage, and shipment of samples must be conducted under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

8.1 Demography and Baseline Assessments

8.1.1 Demographics

The following demographic details will be collected at screening, where permitted by local regulations:

- Sex at birth
- Race
- Ethnicity (for subjects in United States only)
- Age at time of first informed consent

8.1.2 Diagnosis and Disease Status

A subject's history relating to the underlying disease including primary diagnosis, date of diagnosis, as well as disease status at trial entry, staging, and risk category will be recorded.

The following should be recorded at screening for all subjects:

- The primary site of cancer, and initial and current disease stage (TNM staging system).
- The PD-L1 status determined per local assessment using SoC PD-L1 testing per an FDA cleared/approved or CE marked PD-L1 IHC assay
Note: Local assessment is defined as routine testing performed as SoC or as part of the patient's prior treatment, and NOT for the purpose of enrolling in this trial.
- The dMMR or MSI status as per local assessment, if available.

The following should be recorded for subjects with the following types of cancer, if available and as per local assessment:

- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]
- CCI [REDACTED]

Additionally, if known, locally assessed cancer-associated mutations, gene signatures, and immune therapy prognostic targets may also be recorded.

8.1.3 Medical History

Medical history (medical condition [signs, symptoms, and diagnosis], surgical procedure or other events) 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 dose of trial treatment should only be reported if it is an AE assessed by the investigator to be caused by a protocol-mandated procedure (eg, tumor biopsy, 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. See additional reporting details in Section 8.4 and Section 10.2.

Information about recording selected prior laboratory data can be found in Section 8.3.6 and for prebaseline scans in Section 8.2.3.

8.2 Efficacy Assessments

Disease burden must be documented at screening and reassessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of physical examinations, CT scans and other modalities (eg, MRI, brain scans), using RECIST v1.1 (Eisenhauer et al., 2009), Section 10.6).

Importantly, in subjects who discontinue trial treatment without evidence of radiographic PD, tumor imaging must be performed until evidence of radiographic PD, start of new anticancer therapy or death.

8.2.1 Definition of Target and Nontarget Disease

Up to 5 target lesions as per RECIST v1.1 (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. Previously-irradiated lesion(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.

8.2.2 Radiographic Assessments

Efficacy will be assessed based on imaging at screening and on treatment as described in Section 8.2.3.

Guidelines for on-trial imaging and process:

- All subjects will have imaging of the brain, thorax, abdomen, and pelvis performed during screening. CCI [REDACTED]
Imaging of the pelvis is not required for subjects with CCI [REDACTED] but is strongly recommended.
- Tumor imaging is strongly preferred to be acquired by CT with contrast. 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 v1.1, 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 PD. Chest X-rays and ultrasound should not be used to measure tumor lesions.

8.2.3 Assessment of Disease Response and Progressive Disease

- On-trial imaging will be performed at Week 6 (Day 42 $\pm$ 7 days), week 12 (Day 84 $\pm$ 7 days) and every 6 weeks ($\pm$ 7 days) for 50 weeks, and every 12 weeks ($\pm$ 7 days) thereafter from the date of first dose until PD is assessed by the investigator (unless the investigator elects to continue treatment and follow iRECIST beyond RECIST v1.1 PD), the start of new anticancer 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 PD, then a subsequent imaging assessment, in clinically stable subjects only, should be performed within 4 to 7 weeks to confirm PD if following iRECIST. Imaging is not required when subject is in survival follow-up.

- Imaging assessments should be scheduled using the date of first dose as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether trial treatment is temporarily withheld, or unscheduled assessments performed.
- The reading of the scans will be done by a local radiologist. To the greatest extent possible, sites should maintain the same radiologist throughout the trial. Results from the radiology evaluations are to be recorded, and a copy of the evaluation reports should be kept in the subject's file. RECIST v1.1 criteria will be used for endpoint response evaluation ([Eisenhauer et al., 2009](#)) and Section 10.6; iRECIST will be used for exploratory endpoint response evaluation ([Seymour et al., 2017](#)).
- Additional CT scans or MRIs may be performed at the investigator's discretion to confirm response or new symptoms. Tumor imaging to confirm PR or CR must 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.
 - If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.
 - Additional imaging assessments may be performed at any time during the trial at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of PD at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.
- Sites will be required to submit electronic copies of prebaseline scans (since failure of last prior therapy, as available) and all subsequent scans on an ongoing basis to a centralized imaging CRO for exploring the tumor size change and possible independent review of disease assessments for subjects enrolled. Images obtained at an unscheduled timepoint should be documented.
 - Imaging data will be centrally collected and checked for quality by an imaging CRO designated by the sponsor. The local investigator's assessment will be used as primary for the endpoint analyses and for treatment decision making. Central review of the imaging data may be performed if deemed necessary.

8.2.4 *iRECIST Assessment of Disease*

For subjects who continue trial treatment beyond initial RECIST-defined PD v1.1, efficacy assessments must continue.

iRECIST is based on RECIST v1.1 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 PD should be confirmed within 4 to 7 weeks after the first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed PD may continue on-trial treatment until PD is confirmed as long as the subject is clinically stable and has provided written informed consent prior to receiving additional treatment. 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 PD
- Subject is tolerating trial treatment
- Subject must have a stable ECOG PS
- Treatment beyond PD will not delay an imminent intervention to prevent serious complications for PD (eg, CNS metastases requiring immediate treatment).

Any clinically unstable subjects should be discontinued from trial treatment at the first occurrence of radiographic PD. Subjects who 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 iCPD, subjects will discontinue trial treatment. However, if the subject is observed as deriving benefit after iCPD is observed, an exception to continue trial treatment must be approved by the sponsor's medical officer.

If repeat imaging shows iRECIST iSD, iRECIST iPR, or iRECIST iCR, imaging should be continued every 6 weeks (42 ± 7 days) and the subject should continue on trial treatment. Subjects who have repeat imaging to confirm PD do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later.

8.3 Safety Assessments

Any clinically relevant changes occurring during the trial must be documented. Any clinically significant abnormalities persisting at the end of the trial/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached depending on if they correspond to an AE, AESI or and SAE as per Section 8.4.6.

The trial will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities (Section 1.3).

8.3.1 Physical Examination

A complete (full) physical exam (according to SoC) should be performed during the screening period and at the time points specified in the Schedule of Activities (Section 1.3). At subsequent visits, the investigator or qualified designee will perform a brief physical examination as indicated by the subject's symptoms, adverse events, or other findings as determined by the investigator prior to trial treatment administration. After the first dose of trial treatment, new or worsening findings since the last assessment that are considered clinically significant should be documented as AEs.

8.3.2 *Body Measurements*

Height (without shoes) must be measured at screening and rounded to the nearest centimeter or inch. Body weight (without overcoat and shoes) will be measured as indicated in the Schedule of Activities (Section 1.3) and rounded to the nearest kilogram.

8.3.3 *Vital Signs*

Vital signs will be measured supine including temperature (°C or °F) blood pressure (mm Hg), and heart rate (beats/min). Vital signs will be measured as indicated in the Schedule of Activities (Section 1.3).

The subjects should be resting and in a supine or reclined position for at least 10 minutes before vital signs are measured.

Temperature should be measured as an oral, axillary, rectal, or ear temperature. The temperature should be documented as a value corrected according to local standards.

Within each visit, preferably the same equipment shall be used for vital sign measurements.

8.3.4 *Electrocardiograms*

The ECGs will be recorded digitally at the sites by using the standard 12-leads as indicated in the Schedule of Activities (Section 1.3). ECGs are to be taken as triplicate assessments up to C8 in the escalation part (phase 1a and 1b). All other ECGs are to be taken as single assessments.

For the ECG recordings, the subject 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 with the description and time of the occurrence.

ECGs will be performed in accordance with the ECG manual issued by the vendor. Digital ECGs will be transmitted from the sites electronically to a central laboratory for a treatment-blinded measurement of the cardiac intervals and morphologic assessment by a central cardiologist.

The corrected QT interval (QTc) will be calculated using Fridericia's formula:

$$QT_{cF} = \frac{QT}{\sqrt[3]{\frac{RR}{(1s)}}}$$

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 should interpret ECG using the paper ECG reading from the ECG machine, and sign and date the printout. The central reading will be used for trial analysis purposes.

8.3.5 *ECOG Performance Status*

The ECOG PS will be assessed by the investigator as indicated in the Schedule of Activities (Section 1.3). PS will be scored using the ECOG PS scale index (Section 10.5).

8.3.6 *Clinical Laboratory Assessments*

Selected prebaseline laboratory data (ie, LDH, albumin, neutrophils, lymphocytes, platelets, and hemoglobin since failure of last prior therapy), sampled on date(s) concomitant with prior CT scan(s) (alternatively most adjacent date), will be collected to explore correlations with tumor size change kinetics, if available.

Samples will be collected as indicated in the Schedule of Activities (Section 1.3). The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the trial.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

Laboratory test results should be assessed for abnormalities (see Section 10.2 for additional information on reporting of laboratory abnormalities that are considered AEs). When an abnormal laboratory or test result corresponds to a sign/symptom of an already-reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

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

The tests detailed in Table 8-1 will be performed locally. The laboratory reports must be filed with the source documents.

Local laboratory values for biochemistry, hematology and urinalysis must be obtained within 3 days before trial treatment administration and reviewed by the investigator prior to each trial treatment administration to ensure the subject can be dosed according to the dosing instructions defined in the protocol.

Table 8-1 Protocol-Required Safety Local Laboratory Assessments

Hematology (local)	Biochemistry (local)		Urinalysis (local)
hematocrit	ALT	glucose	leukocytes
hemoglobin	albumin	LDH	protein
platelet count	alkaline phosphatase	lipase	
RBC count	amylase	magnesium	
RBC indices:	AST	phosphate	
• MCH	BUN	sodium	
• MCHC	calcium	total and direct bilirubin	
• MCV	chloride	total protein	
• % reticulocytes	C-reactive protein	uric acid	
WBC count with differential:	creatinine (and estimated CrCl/GFR) ^a		
• basophils	GGT		
• eosinophils			
• lymphocytes			
• monocytes			
• neutrophils			
	Viral serology^c	Endocrine/Thyroid function	Other
	HBV HIV	T3 ^d TSH	
	HCV HTLV-1	T4	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta-human chorionic gonadotropin; BUN=blood urea nitrogen; C1D1=Cycle 1 Day 1; CrCl=creatinine clearance; eGFR=estimated glomerular filtration rate; GFR=glomerular filtration rate; GGT=gamma-glutamyltransferase; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HTLV-1=human T-lymphotropic virus type 1; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; MDRD=Modification of Diet in Renal Disease; RBC=red blood cell; Scr=serum creatinine; T3=total triiodothyronine; T4=free thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell.

- Estimate creatinine clearance using MDRD ($eGFR = 186 \times (SCr - 1.154) \times (age - 0.203) \times (0.742 \text{ if female})$).
- A serum pregnancy test should be performed during the screening period (within 7 days of C1D1). Additionally, a urine or serum test should be performed within 24 hours of dosing at the start of each subsequent cycle. If a urine pregnancy test is positive, a serum pregnancy test is required to confirm.
- Only performed if required by local regulations.
- Free T3 is acceptable if considered local standard.

8.4 Adverse Events and Serious Adverse Events

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 SOPs 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.

Information in this section should be used in conjunction with the additional details provided in Section 10.2.

8.4.1 Definition of Adverse Events and Serious Adverse Events

The definitions of AEs, SAEs, AESIs, as well as attribution definitions; severity criteria; and procedures, are provided in Section 10.2.

8.4.1.1 *Adverse Events of Special Interest*

No AESIs have been identified for GEN1055 based on nonclinical data.

8.4.1.2 *Other Events of Interest*

Infusion-Related Reactions

IRRs are defined as any AE occurring during infusion or where the onset of the event occurs within 24 hours after ended infusion. For IRRs, the causality of the event should be judged as “related” by the investigator.

Investigators should consider the clinical picture and isolated events, such as “fatigue,” occurring within 24 hours after the end of infusion and assess whether they do or do not constitute an IRR (refer to Section 6.8.2.3 for further IRR treatment guidance).

Immune-Mediated Adverse Reactions

Investigators will be asked to provide an assessment of whether an AE is an immune-mediated adverse reaction or not, and to provide a rationale for the assessment, such as a description of the response to immunosuppressive or other therapy, rechallenge information, clinicopathologic results, increase in frequency or severity of immune-mediated adverse reaction with a pattern suggesting synergism, or other.

8.4.2 *Adverse Event Reporting*

The safety reporting periods are defined in Table 8-2. The safety reporting period starts once the subject has signed the ICF and ends when the subject completes the last safety follow-up visit, withdraws consent, starts new anticancer treatment, or dies, whichever comes first.

Table 8-2 Reporting Period and Requirements

Safety Reporting Period	Reporting Requirements
Signing of ICF until first dose of trial treatment	AEs, if assessed by the investigator to be related to a protocol-mandated procedure (eg, tumor biopsy, CT scan), including washout or discontinuation of prior medications.
First dose through SFU1 and SFU2	All AEs (see definitions in Section 10.2), regardless of causality, will be documented.
After the last safety follow-up visit through end of trial/after end of trial	There is no requirement to monitor subjects for SAEs following the protocol-required safety reporting period or after end of trial. However, if the investigator becomes aware of an SAE, it must be reported if judged by the investigator as related to trial treatment.
Refer to Section 10.2.2 for additional guidance for recording and reporting AEs and Section 7.1.2 for timing of safety follow-up visits.	

AE=adverse event; CT=computed tomography; ICF=informed consent form; SAE=serious adverse event; SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2.

NOTE: Any second primary malignancy(ies) regardless of relatedness to trial treatment, should be reported as an SAE at any time during or after the trial if the investigator becomes aware of such an event (see Section 8.4.3.1).

For details regarding follow-up of AEs and SAEs, see Section 8.4.6. Refer to Section 6.3 for guidance regarding product complaints.

8.4.3 Events Requiring Immediate Reporting

Refer to Section 10.2.2 for additional guidance for recording and reporting AEs.

8.4.3.1 Second Primary Malignancy

Second primary malignancy(ies) (not a metastasis of the cancer under trial), regardless of relatedness to trial treatment, must be reported to the sponsor within 24 hours of knowledge of the event (at any time during or after the trial). Second primary malignancies should be reported as SAEs.

8.4.3.2 Serious Adverse Events

All SAEs occurring during the safety reporting period must be reported from the trial site to the sponsor no later than 24 hours via EDC following:

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

8.4.3.3 Overdose/Medication Errors

Overdoses are defined in Section 6.9. All cases of overdose with trial treatment, whether associated with an AE or not, must be reported to the sponsor within 24 hours of knowledge of the event (see additional details in Section 6.9).

Overdose of concomitant medication should only be reported if associated with AEs whether serious or not.

Medication errors (including infusion rate errors) and uses outside what is foreseen in the protocol, including misuse and abuse of the IMP or AMP, whether associated with an AE or not, should be reported to the sponsor within 24 hours of knowledge of the event. Medication errors related to concomitant medication should only be reported if associated with AEs whether serious or not.

8.4.3.4 Pregnancy

Pregnancy is not allowed in this trial. However, if any pregnancy occurs during trial participation, the pregnancy must be reported using the pregnancy reporting paper form available in the investigator site file.

All reports of pregnancy, occurring during the trial or 6 months after receiving the last dose of GEN1055 and per Section 10.3 after the last dose of trial drug, 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 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 IMPs and AMPs must be promptly reported to the 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.

8.4.3.5 Adverse Events of Special Interest or Other Events of Interest

Not applicable to this trial.

8.4.4 Regulatory Reporting Requirements

8.4.4.1 Regulatory Reporting Requirements for SUSARs

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(s) 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 8.4.3.2).

The sponsor will ensure that all relevant information about SUSARs is documented and reported as soon as possible, but within a maximum of 15 calendar days (fatal or life-threatening SUSARs within a maximum of 7 calendar 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 within the required reporting timelines. The sponsor will also communicate relevant information on SUSARs with the investigators in predefined periods and according to local regulations.

The investigator should be aware of local reporting regulations to the IEC/IRB. The 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. For SUSARs aggregated in a line listing distributed quarterly, or every 6 months, or in periods as warranted by the IEC/IRB; the investigator must review such safety information in a timely manner and signoff for the review as instructed by the sponsor, to document the awareness about the latest safety updates that may impact on the investigator's responsibilities for subject care.

8.4.4.2 Regulatory Reporting Requirements for AMPs

Where an AE is suspected to be related only to an AMP, and does not result from a possible interaction with the IMP, safety reporting will be done by the sponsor in accordance with Chapter 3 of TITLE IX of Directive 2001/83/EC.

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

The following should not be reported as an AE or SAE:

- Events that are clearly consistent with the expected pattern of the underlying disease or 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 may be reported as AEs or SAEs if the symptoms 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.
- Hospitalization due solely to progression of the underlying cancer should not be reported as an SAE. See Section 10.2.1.2, under the definition of SAE, for additional reasons when hospitalizations should not be reported as SAEs.
- Unrelated Procedures: Diagnostic and therapeutic noninvasive 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 (eg, an acute appendicitis should be reported as the AE and not the appendectomy).

8.4.6 *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 anticancer treatment, whichever comes first.

All SAEs and events qualifying for immediate reporting (see Section 8.4.3) that are ongoing at the safety follow-up visit(s) 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.

8.4.7 *Precautions and Warnings*

Refer to the IB for detailed information for precautions and warnings for GEN1055. Additional relevant safety information collected between IB updates will be communicated in the form of investigator notifications. Significant information will be included in the ICF and should be discussed with the subject during the trial.

For approved IMP and AMP products used in combination with GEN1055, reference the current prescribing information (eg, USPI, SmPC) for additional safety information.

8.5 Pharmacokinetics

Blood samples will be collected and processed to obtain serum, to evaluate the PK of GEN1055 at the time points specified in the Schedule of Activities (Section 1.3). The actual date and time of each sample collection must be recorded.

Samples will be analyzed to determine concentrations of GEN1055 using a validated, specific, and sensitive bioanalytical method by or under the supervision of the sponsor.

Samples collected for analyses of GEN1055 serum concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period which could mean after the trial is closed. Additional samples may be collected during unscheduled visits if warranted and agreed upon between investigator and sponsor, eg, for safety monitoring.

Additional information about the collection, handling, and shipment of samples is included in the laboratory manual.

8.6 Biomarkers

8.6.1 Biomarker Sample Collection

Samples for biomarker analyses will be collected as specified in the Schedule of Activities (Section 1.3). 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.

Details on the collection, processing, storage, and shipment of biomarker samples will be provided in separate documents (eg, sample flowchart and/or laboratory manual).

All biopsies performed in this trial will be done by trained medical staff including specialized radiologists or surgeons depending on the location of the lesion and according to the local SoC. Lesions will be selected by the investigator or the radiologist with the best interest of the subject in mind. Biopsies will only be done if there is a low risk of complications for the subject.

8.6.2 Biomarker Assessments in Tumor Samples

A biopsy collected before administration of trial treatment (ie, during the screening period) is mandatory for all subjects with accessible tumors. A fresh biopsy taken during the screening period is preferred, unless medically unfeasible and reviewed and approved by the sponsor. If this cannot be provided, a biopsy taken after failure/stop of last prior treatment and taken within 6 months prior to C1D1 may be provided. The biopsy can be a whole lymph node, core tumor biopsy or resected tissue. A fine needle biopsy or aspirates will not be sufficient. Specimen types that are not acceptable tumor tissue samples are cytological specimens, aspirates, bone, or bone marrow. All tumor biopsies should be FFPE. Details for the preparation and number of slides will be described in the laboratory manual.

During the trial, an on-treatment biopsy is also required, between C2D8 and C3D1, as described in [Table 1-3](#) and [Table 1-7](#), unless medically unfeasible and reviewed and approved by the sponsor. Any additional tumor biopsies collected that are part of normal clinical practice will also be examined as described below.

Biomarker analyses in tumor samples at baseline and during treatment with trial treatment may help confirm trial treatment's mode of action and enable the identification of biomarkers predictive of response to trial treatment. Tumor biopsies will be evaluated for target expression (protein or RNA), as well as molecular profiling to identify potential mechanisms of tumor response and/or treatment-induced changes in the immune microenvironment.

8.6.2.1 Protein Expression Analyses

Expression of proteins related to malignant solid tumor biology or trial treatment's mode of action 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 exploratory digital pathology analyses.

8.6.2.2 RNA Expression Analyses

RNA sequencing may be performed on tumor biopsies to determine OX40 RNA expression levels, as well as to evaluate other potential genes associated with OX40 biology, with immune effector cell activation, or with cancer biology in general. Tumor biopsies may be used to collect transcriptomic information from defined tumoral regions of interest, using digital profiling transcriptomic platforms.

8.6.2.3 DNA Analyses

Tumor biopsies may also be analyzed using NGS for analyses of DNA mutations, copy number variations, microsatellite instability, indels, and/or rearrangements or polymorphisms in genes associated with OX40 expression or function, and/or trial treatment's proposed mode of action, or cancer biology. Additional analyses may be conducted if it is hypothesized that this may help resolve issues with the clinical data.

A whole blood sample may also be evaluated to confirm the tumor specificity of any genomic alterations that are identified. Where required by local or country-specific regulations, each subject must sign a separate ICF indicating agreement to provide samples for the required genomic biomarker analysis (DNA).

8.6.3 Biomarker Assessments in Blood Samples

Biomarker assessments may also be performed using whole blood samples to investigate potential pharmacodynamic markers, including OX40 receptor occupancy before and after treatment with GEN1055, changes on T-cell receptor clonality profile, and explore the relationship to the efficacy and/or mode of action of trial treatment. Assessments will be performed in samples collected 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.

8.6.3.1 *Immunophenotyping Analyses*

Immunophenotyping may be performed on whole blood and PBMCs (eg, measurement of T cells, B cells, NK cells) at baseline and during treatment at planned visits so changes associated with the mode of action of trial treatment, subject response to trial treatment, and disease biology can be evaluated. In addition, the OX40 receptor occupancy at baseline and during treatment with GEN1055 will be monitored.

8.6.3.2 *Cytokine (Soluble Factors) Analyses*

Analysis of cytokines and other soluble factors, including soluble OX40, will be performed at baseline and during treatment at planned visits to investigate safety and potential pharmacodynamic markers of trial treatment.

8.6.3.3

CCI

CCI

8.6.3.4

CCI

CCI

8.7 Immunogenicity

Venous blood samples will be drawn for analysis of ADAs as per the time points specified in the Schedule of Activities (Section 1.3).

Serum samples will be screened for ADAs binding to GEN1055 and the titer of confirmed positive samples will be reported. Serum concentrations of GEN1055 will be analyzed (see Section 8.5) and those data will be used to for interpretation of the ADA data. The ADA samples 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. Subject confidentiality will be maintained.

Neutralization characterization of ADAs may also be performed using appropriate methods.

Further details are included in the laboratory manual.

9 STATISTICAL CONSIDERATIONS

The statistical analysis of the data collected in this trial is the responsibility of the sponsor. A description of the statistical methods to be used to analyze the data is outlined below. The analyses for the expansion part will be detailed further in the SAP.

9.1 Statistical Hypotheses

There is no formal hypothesis to be tested in the dose escalation nor in the expansion part.

The expansion part will collect data to establish proof-of-activity.

9.1.1 Multiplicity Adjustment

N/A as no hypothesis testing is planned.

9.2 Population for Analyses

Analysis Set	Definition
Full Analysis Set	Monotherapy: Subjects enrolled and treated with at least 1 dose of GEN1055. Subjects are analyzed according to actual treatment (dose level). Combo: Subjects enrolled and treated with at least 1 dose of each of GEN1055 and pembrolizumab. Subjects are analyzed according to actual treatment (dose level).
Safety Set	Monotherapy: Subjects enrolled and treated with at least 1 dose of GEN1055. Subjects are analyzed according to actual treatment (dose level). Combo: Subjects enrolled and treated with at least 1 dose of each of GEN1055 and combination product(s). Subjects are analyzed according to actual treatment (dose level).
Dose-Determining Analysis Set	The DDS is relevant for the dose escalation part only and consists of all subjects from the Safety Set who meet the minimum exposure criteria for Cycle 1 and have either completed the DLT observation period or have experienced a DLT during Cycle 1. A subject on monotherapy is considered to have met the minimum exposure criteria for Cycle 1 if trial treatment has been administered for 80% to 125% of the planned dose of GEN1055. A subject on combo is considered to have met the minimum exposure criteria for Cycle 1 if trial treatment has been administered for 80% to 125% of the planned dose of each of GEN1055 and combination product(s).
Response Evaluable Set	The response evaluable set consists of all subjects who have baseline evaluable disease according to RECIST v1.1 and at least 1 postbaseline disease assessment. It also includes subjects who die or are withdrawn from treatment due to clinical progression before the first response assessment; these subjects are treated as nonresponders.
Pharmacokinetic Analysis Set	The pharmacokinetic analysis set will include all subjects who receive at least 1 dose of GEN1055 and who provide at least 1 evaluable PK sample for GEN1055.
Immunogenicity Analysis Set	The immunogenicity analysis set will include all subjects who receive at least 1 dose of GEN1055 and have a baseline and at least 1 evaluable on-treatment ADA sample.

ADA=anti-drug antibody; DDS=dose-determining analysis set; DLT=dose-limiting toxicity;
PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumours.

9.3 Statistical Analyses

This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

The SAP for the expansion part will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section.

9.3.1 General Considerations

Data from the dose escalation and expansion parts will be presented separately.

Data from monotherapy and combination therapy in dose escalation will be presented separately.

Data from each cohort in the expansion part will be presented separately, if not otherwise specified.

Descriptive statistics will be provided for selected demographics, safety, PK and biomarker data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Data will be presented and summarized by treatment and dose regimen, and time, as appropriate.

Baseline is the last available measurement prior to first dosing, if not otherwise specified.

9.3.2 Analysis of the Dose Escalation Part

9.3.2.1 Primary Endpoint Analysis

The primary endpoints for the dose escalation part of the trial are the incidence of AEs and the incidence of DLTs. For reporting of AEs see Section [9.3.5](#).

The incidence of DLTs will be presented for the DDS using descriptive statistics.

9.3.2.2 Secondary Endpoint Analysis

For the dose escalation part of the trial the following secondary endpoints are presented.

Pharmacokinetics

For reporting of PK concentrations and parameters see Section [9.3.6.1](#).

PK data may also be used for PK/pharmacodynamic modeling. Results of such modeling efforts will be reported separately.

Immunogenicity

Immunogenicity will be presented as described in Section [9.3.6.2](#).

Response

The response evaluable set will be used for presentation of response.

Objective Response Rate

ORR as assessed by investigator by RECIST v1.1 will be summarized as described in Section 9.3.3.1.

Both confirmed responses and confirmed/non-confirmed responses will be presented.

Duration of Response:

DoR based on investigator assessment is defined as the time from the first documentation of response (CR or PR) to the date of PD or death, whichever occurs earlier. DoR will be analyzed as described for PFS in Section 9.3.3.2. Confirmed response will be used.

Time to Response

TTR based on investigator assessment is defined as the time from C1D1 to first documentation of objective response (CR or PR) in subjects achieving PR or CR. Time to response will be analyzed as described for PFS in Section 9.3.3.2. Confirmed response will be used.

Disease control rate

The DCR is defined as the proportion of subjects with BOR of CR, PR, or SD.

The estimated DCR and the exact 2-sided 95% confidence interval using the Clopper-Pearson method will be presented.

Both confirmed responses and confirmed/non-confirmed responses will be presented.

9.3.3 Analysis of the Expansion Part

9.3.3.1 Primary Endpoint Analysis

The primary endpoint for the expansion part of the trial is the confirmed ORR as assessed by investigator and classified as per RECIST v1.1. The ORR is defined as the proportion of subjects with BOR of CR or PR. All other categories, including not evaluable, are considered non-response.

BOR will be summarized in conjunction with the ORR. The estimated ORR and the exact 2-sided 95% confidence interval using the Clopper-Pearson method will be presented.

All responses, ie confirmed and unconfirmed, will be summarized.

In addition, for subjects on combination therapy, if multiple dose regimens are included in the ECs, objective response will be analyzed for each cohort/indication by logistic regression including dose regimen as a factor. Odds ratios for the effect of dose regimens will be estimated with associated 95% likelihood ratio-based confidence interval. Similar analysis across the ECs/indications will be done, including cohort as an additional term in the logistic

regression model, providing an overall estimate of the effect of dose regimen. In addition, ORR in each cohort will be estimated for each dose regimen with exact 95% confidence intervals.

9.3.3.2 Secondary Endpoint Analysis

Duration of Response

DoR based on investigator evaluation will be presented as described for the dose escalation part of the trial and will be analyzed as described for PFS, below. Confirmed response will be used.

Time to Response

TTR based on investigator evaluation will be presented as described for the dose escalation part and will be analyzed as described for PFS, below. Confirmed response will be used.

Disease control rate

The DCR is defined as the proportion of subjects with BOR of CR, PR, or SD.

The estimated DCR and the exact 2-sided 95% confidence interval using the Clopper-Pearson method will be presented.

Both confirmed responses and confirmed/non-confirmed responses will be presented.

Progression-Free Survival

PFS is defined as the time from C1D1 to first documented PD or death due to any cause, whichever occurs earlier. PFS will be censored similar to table C1 in Appendix C in the FDA Guidance for Industry: **CCI** [REDACTED].

PFS will be defined for all subjects and presented graphically as well as summarized using survival analysis methods in terms of Kaplan-Meier estimates.

PFS will be assessed by investigator by RECIST v1.1.

Overall Survival

OS is defined as the time from C1D1 to the date of death due to any cause. Subjects who withdraw consent to the trial or are lost to follow-up will be censored at the latest date the subject was known to be alive (on or before the cutoff date).

OS is presented as described for PFS.

Immunogenicity

Immunogenicity will be presented as described in Section 9.3.6.2.

Incidence of AE

AEs will be presented as described in Section 9.3.5.

Pharmacokinetics

For reporting of PK concentrations and parameters see Section 9.3.6.1.

9.3.3.3 *Efficacy Monitoring in Expansion Cohorts*

As up to 80 subjects with CCI could potentially be enrolled, efficacy monitoring has been applied for each of EC3 and EC4. The 2 CCI cohorts will be separately evaluated for efficacy using the PPoS method (Lee and Liu, 2008) when data from the first 20 subjects are available in the given cohort. Further characteristics of this approach are dependent on the number of dose regimens selected for the ECs based on results of phase 1a and 1b.

9.3.4 *Exploratory Endpoint(s) Analyses*

Exploratory endpoint analyses for the expansion will be detailed in the SAP.

9.3.5 *Safety Analyses*

Safety analysis will be done for both escalation and expansion part of the trial.

The Safety Set will be used.

Adverse Events

The on-treatment period is defined as the time from C1D1 until the end of last safety follow-up.

TEAEs are events that occur during the on-treatment period or AE starting before C1D1 and worsening during the on-treatment period.

AEs will be graded according to the NCI-CTCAE as described in Section 10.2.3.1.

All TEAEs and treatment-emergent SAEs will be presented descriptively.

Analysis of AEs will be summarized using the Safety Set with the exception of deaths, which will be presented for the FAS.

Clinical Laboratory Tests

Grading of laboratory values will be assigned programmatically according to the NCI-CTCAE (see Section 10.2.3.1). The calculation of NCI-CTCAE grades will be based on the observed laboratory values only; clinical assessment will not be considered. CTCAE grade 0 will be assigned for all non-missing values not graded 1 or higher.

Laboratory tests that are graded by NCI-CTCAE will be presented in a shift table presenting baseline grade vs worst on-treatment grade.

Laboratory tests that cannot be graded by NCI-CTCAE will be presented in a shift table presenting baseline low/normal/high classification vs worst on-treatment value.

The number of subjects with at least 1 grade 3 or higher on-treatment laboratory test will be summarized.

ECOG PS

ECOG PS will be presented descriptively.

ECG

Evaluation of ECG by investigator will be presented as normal/abnormal not clinically significant/abnormal clinically significant.

ECG measurements (eg QTc) will be presented by visit and timepoint. Abnormal values as read by central reader will be presented descriptively.

Vital Signs

Number of subjects with at least 1 clinically notable abnormal value will be presented.

9.3.6 *Other Analyses*

Subgroup analysis for the primary endpoint in the expansion part of the trial may be explored to investigate whether the treatment effect is consistent across various subgroups.

9.3.6.1 *Pharmacokinetic Analysis*

Dose Escalation Part and Expansion Part

Individual curves of concentrations of GEN1055 against time, including information on actual dose, will be presented for all subjects. All available data will be shown in these figures. PK endpoints will be calculated based on non-compartmental methods for each subject and each cycle in which a full PK profile is taken, if feasible. Predose and end-of-infusion values will be summarized for all trial days where measured.

Descriptive statistics of PK endpoints will include arithmetic and geometric means, standard deviation, %CV, median, minimum, and maximum. Concentration values below the LLOQ will be handled as LLOQ/2 in summary statistics and reported as is in data listings. Any missing PK endpoint data will not be imputed.

The PK analysis set will be used.

9.3.6.2 *Immunogenicity Analyses*

The results from the analysis of immunogenicity samples are given as ADA positive, ADA negative, or missing. The ADA positive results are then to be confirmed with a given titer value.

Data will therefore be categorized as 1 of the following:

- ADA confirmed
- ADA not confirmed (ie, negative samples and not-confirmed positive samples)

- Missing

The number of subjects having at least 1 confirmed ADA during treatment will be presented and the largest titer value will be presented for subjects having at least 1 confirmed ADA sample. The immunogenicity analysis set will be used for immunogenicity analyses.

9.3.7 *Planned Analyses*

9.3.7.1 *Interim Analysis*

An interim analysis is not planned for this trial.

9.3.7.2 *Primary Analysis*

The primary analysis will be conducted when all subjects have discontinued treatment and have completed all required follow-up visits. At this time, a final data sweep will be performed to determine the survival status of previously discontinued subjects.

9.4 *Sample Size Determination*

No formal sample size calculations were done for the dose escalation part.

For monotherapy (ie, phase 1a) it is expected to have 6 DLs (Section 4.1.1) in the escalation and with an average of 6 subjects per DL (ranging from 1 to 9 subjects) and approximately 9 additional subjects for backfilling, a total of 50 subjects is considered adequate.

For combination therapy (ie, phase 1b) it is expected to have 3 DLs (Section 4.1.2) in the escalation and with expected 12 subjects, including backfilling subjects per DL a total of 40 subjects is considered adequate.

No formal sample size calculations were done for the expansion part (phase 2a).

10 APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 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.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects.

10.1.2 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 ensure that a qualified, trained deputy physician is available for medical care of the subjects. The investigator shall notify the sponsor immediately of any serious breach of ICH GCP E6(R2), the protocol, or any regulation where required.

10.1.3 Independent Ethics Committee or Institutional Review Board

This trial will be undertaken only after the IEC/IRB has given written approval of the final protocol, amendments to the protocol (if applicable), the ICF, subject identification card, 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 written 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 noncompliance, 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 review(s) of trial progress will be submitted by the investigator, where applicable, to the IEC/IRB at intervals stipulated in its guidelines.

At the end of the trial, the investigator (or sponsor where required) will notify the IEC/IRB about the trial completion, within the required timelines.

10.1.4 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.

10.1.5 Administrative Procedures

10.1.5.1 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/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects or changes that involve logistical or administrative aspects only (eg, change in the sponsor's medical officer 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 will be 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.

10.1.5.2 Regulatory Documentation

This protocol and any amendments 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.

10.1.5.3 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 unique subject identifier.

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.

10.1.6 Informed Consent Process

The ICF(s) that is/are used must be approved 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 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. If alternative treatments are available, subjects will be informed in both parts of the trial. Refusal by a subject to take part will not prejudice future treatment. 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 IRB/IEC and Regulatory 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 is authorizing such access, including permission to obtain information about survival status, and agrees to allow their trial physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about survival status.

The subject will be given sufficient time to read the ICF and the opportunity to enquire 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 documented by means of either the subject's or their legally acceptable representative's personally dated signature.

Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, European regulation 536/2014 for clinical studies, local regulations, ICH guidelines, HIPAA, and EU GDPR 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 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 is obtained.

The sponsor will, on an ongoing basis, assess whether reconsent of subjects is needed.

A separate ICF will be used for the required DNA/RNA research component of the trial if required by local regulations.

10.1.7 Data Protection

The investigator will ensure that the confidentiality of all 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 ICF 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 are only stored on IT systems and networks that are protected against virus, malware, and unauthorized access.
- Data are 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 are encrypted when at rest.
- Data have 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 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 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 such 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 was involved, what security measures were in place (for instance, if the data was encrypted or pseudonymized), 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.

10.1.8 Committees Structure

Dose Escalation Committee

The DEC will be chaired by the sponsor's medical officer (or delegate) and membership will include investigator(s), a sponsor clinical research scientist, a safety physician, a statistician, a clinical pharmacologist, and other sponsor staff, as appropriate. The DEC will meet at regular frequency throughout the dose escalation part and during the safety run-in period of specific ECs, as per DEC charter. Ad hoc meetings may be held if deemed necessary

The schedule of DEC meetings will depend on the completion of DLT(s) evaluation period(s).

All available data, including but not limited to safety, PK, and pharmacodynamic data, covering the DLT evaluation period will be reviewed by the DEC. Cumulative data from treatment doses after the DLT period may also be monitored. Recommendations on dose escalation (or de-escalation) and for the safety run-in will be made by the DEC to the Safety Committee.

Safety Committee

The sponsor's Safety Committee is a cross-functional committee that evaluates the evolving safety profile of the product, supports assessment of the product's benefit/risk profile and recommends risk management strategies to ensure safety of subjects who participate in Genmab-sponsored clinical trials or patients treated with marketed Genmab drugs. For the FIH dose escalation phases 1a and 1b, the Safety Committee will consider the

recommendation made by the DEC and make the final decision regarding dose escalation (or de-escalation). The Safety Committee can also stop further enrollment if treatment-emergent toxicity is determined to result in an unfavorable change in subject benefit/risk. Enrollment may be temporarily held, if needed, for the Safety Committee to evaluate the emerging data.

Decisions will be communicated to investigators and decisions with the potential to affect subject safety (eg, unfavorable change in benefit/risk assessment) will be promptly communicated to investigators and regulatory authorities, as required.

10.1.9 *Dissemination of Clinical Trial Data*

The protocol information will be registered in a publicly accessible database (eg, clinicaltrials.gov, CTIS, and/or other national registries/Health Authority websites). In addition, after trial completion (defined as last subject last visit globally) and finalization of the study report, 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, CTIS).

10.1.10 *Data Quality Assurance, Record Retention, Monitoring, and On-Site Audits*

10.1.10.1 *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 sponsor's delegate), and direct transmission of clinical laboratory data from a central laboratory, (ECG data from the ECG vendor, and review of radiographic scans, pathology reports [as applicable] from the central imaging vendor [expansion only]) 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 or remote 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, the data will be reviewed for accuracy and consistency with the data sources.

10.1.10.2 *Record Retention*

In compliance with ICH GCP E6(R2), 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. Medical Records (subjects' hospital record) is retained/archived according to applicable local regulation.

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 qualified and trained 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.

10.1.10.3 Monitoring

The sponsor will use a combination of remote and on-site monitoring to monitor this trial. The sponsor or delegate 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 verify 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, or 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 with 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 contact 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.

10.1.10.4 On-Site Audits and Inspections

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 designee(s).

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 they have been contacted by a regulatory agency concerning an upcoming inspection. Regulatory inspectors must be allowed direct access to original medical records (source data/documents).

10.1.11 Source Documents and Case Report Form Completion

10.1.11.1 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. Limited redacted source documents can be shared with the sponsor during screening for eligibility determination, where permitted by local regulations. 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/subject/randomization number (if applicable)
- 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 treatment discontinuation/trial 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 some cases, eg, demographic data (race, ethnicity, sex at birth), the eCRF may be considered the subject's source documentation.

In addition to the source data in medical records, data may be recorded directly electronically (eg, ECGs, PROs). 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.

10.1.11.2 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 will be transmitted in a secure manner to the sponsor within agreed upon time frames.

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, preferably within 5 days. 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 data entry can be done as follows (corrections 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):

- 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 the trial-site personnel.

10.1.12 Trial and Site Start and Closure

The trial start date will be the first act of recruitment (ie, the first subject that signs the informed consent form).

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 GEN1055 development.

The sponsor may, based on available data, discontinue further development of GEN1055.

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(s) and should ensure appropriate subject therapy and/or follow-up.

10.1.13 Publication Policy

All information, including but not limited to information regarding GEN1055 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 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 GEN1055, and thus may be shared as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical trial to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

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, 2023](#)) the sponsor in

conjunction with any collaborative group(s), shall have the right to publish such primary (multicenter) data and information as per the prespecified 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.

10.2 Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, and Reporting

10.2.1 Definitions

10.2.1.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or 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.

10.2.1.2 Definition of Serious Adverse Event

An SAE is defined as an AE that meets 1 of the following criteria:

- Is fatal or life-threatening
 - 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 were more severe.
- 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 1 of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization.
 - Hospitalizations for the following reasons should not be reported as SAEs:
 - Routine treatment or monitoring of the underlying disease, not associated with any deterioration in the condition
 - Solely due to progression of the underlying cancer
 - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the underlying disease and has not worsened since signing the ICF
 - 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.

10.2.1.3 Definition of Adverse Events of Special Interest

AESIs are defined as events (serious or nonserious) 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 8.4.1.1 and the IB.

10.2.2 Procedures for Recording and Reporting

10.2.2.1 Recording

All AEs, serious or nonserious, must be documented as outlined in [Table 8-2](#).

- 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 an individual AE.
- 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.

Laboratory 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 for the abnormality is found.
- *NOTE: An NCI-CTCAE grade 3 or 4 laboratory abnormality does not automatically indicate an SAE.*

10.2.2.2 Reporting

The primary mechanism for reporting an SAE to the sponsor is the EDC tool. In order to report pregnancies and if the EDC tool is unavailable to report SAEs, then the site must use the respective paper report forms via secure transmission to ensure the event is reported within 24 hours following first knowledge of the event.

Once the trial has ended, if the investigator learns of a second primary malignancy or treatment-related SAE, the event should be reported using the paper forms via secure transmission.

10.2.3 *Evaluation of Adverse Events*

10.2.3.1 *Severity*

Toxicities will be graded for severity according to the NCI-CTCAE, v5.0. Exceptions are CRS and ICANS events, which are to be graded by ASTCT criteria ([Lee et al., 2019](#)).

10.2.3.2 *Relationship to the Trial Treatment*

Any AE assessed as related to either IMP or AMP is considered a treatment-related AE.

The investigator must assess whether or not the event is related to the trial treatment. If a subject is on combination treatment, this assessment should be done separately for each IMP and AMP. 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 treatment caused the AE, this means there is evidence to suggest a causal relationship between the trial treatment and the AE (ie, considered related). Refer to the GEN1055 IB and prescribing information for pembrolizumab and AMPs.

10.2.4 *Annual Safety Reporting by Sponsor*

Within the EU, the sponsor will submit an Annual Safety Report for GEN1055, including data on multi-drug therapy.

10.3 Appendix 3: Definition of Reproductive Potential and Contraception

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 the trial and for 6 months after the last GEN1055 administration; all men must also refrain from donating sperm during the trial and for 6 months after receiving the last dose of GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice.

Female subjects of reproductive potential must agree to use adequate contraception during the trial and for 6 months after receiving the last dose of GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice. Adequate contraception is defined as highly effective methods of contraception (see [Table 10-1](#)). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year when used consistently and correctly.

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 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 GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice.

Table 10-1 Highly Effective Methods of Contraception

- | |
|---|
| <ul style="list-style-type: none"> • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation^a: <ul style="list-style-type: none"> ○ Oral ○ Intravaginal ○ Transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation^a: <ul style="list-style-type: none"> ○ Oral ○ Injectable ○ Implantable^b • Intrauterine device^b • Intrauterine hormone-releasing system^b • Bilateral tubal occlusion^b • Vasectomized partner^{b, c} • Sexual abstinence^d |
|---|

Adapted from “Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1.” ([CTFG, 2020](#)).

- a. Hormonal contraception may be susceptible to interaction with trial treatment, which may reduce the efficacy of the contraception method, and therefore must be supplemented with a barrier method for non-vasectomized male partner (preferably a condom with spermicidal foam/gel/film/cream/suppository).
- b. Contraception methods that, in the context of this guidance, are considered to have low user dependency.
- c. Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the female subject of reproductive potential (ie, the trial subject) and that the vasectomized partner has received medical assessment of the surgical success.
- d. 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 treatment. 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.

Specific requirements for Japan are provided in Section [10.10.2](#).

10.4 Appendix 4: Sample Storage and Destruction

Any sample collected according to the Schedule of Activities (Section 1.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to trial subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the trial. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded before being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the trial. Results are stored in a secure database to ensure confidentiality.

Exploratory biomarker research may also be performed to investigate and better understand malignant solid tumors, the dose response and/or prediction of response to GEN1055, and characterize aspects of the molecule (eg, MoA/target, metabolites). Results from this analysis are to be documented and maintained; but are not necessarily reported as part of this trial. Samples can be retained for up to 5 years after the last subject receives the first dose of trial treatment. Samples will be destroyed after the 5-year retention period.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of any exploratory biomarker research are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the Investigator. Following the request from the subject, the Investigator is to provide the Sponsor with the required trial and subject number so that any remaining samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples before the request for destruction will be retained by Genmab.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the Investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 10.1.7 for subject confidentiality.

10.5 Appendix 5: 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.

Source: ([Oken et al., 1982](#))

10.6 Appendix 6: RECIST (v1.1) Criteria Summary

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	
Term	Definition
Complete response (CR)	All of the following: - Disappearance of all target and non-target tumor lesions AND - Reduction in short axis to <10 mm in all pathological target and non-target lymph nodes* AND - Normalization of tumor marker level (if applicable)
Partial response (PR)	≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least 1 of the following: ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir; this includes the baseline sum if that is the smallest on trial) AND an absolute increase of ≥5 mm in the sum of diameters OR - Unequivocal† appearance of 1 or more new lesion(s) OR - Unequivocal progression of non-target lesions‡
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters (nadir) while on trial.

Note: A measurable lesion must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness no greater than 5 mm).

* When lymph nodes are included as target lesions, the sum of lesions may not reach 0 mm even if CR criteria are met, since a normal lymph node is defined as having a short axis <10 mm.

† Not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (healing or flare of pre-existing lesions).

‡ Modest increases in the size of 1 or more non-target lesions are not considered unequivocal progression.

From RECIST v1.1 ([Eisenhauer et al., 2009](#)).

A response (CR or PR) will be considered confirmed if the following response assessment (4-6 weeks after the initial response) still shows response (CR or PR). In cases where the initial response is followed by SD, it will be considered as confirmed if the SD is later followed by PR or CR. For example, if a subject had PR in week 6, SD in week 12, and PR in week 18, this PR will be considered as confirmed.

10.7 Appendix 7: Management of Cytokine Release Syndrome

CRS Grade	Management
1	Fever: Subjects with a new fever should be admitted to the hospital if not already. Investigate for infection and rapidly start up broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until any potential neutropenia resolves. Constitutional symptoms may be helped by NSAIDs. Tocilizumab: No*. Steroids: No.
2	Fever: As per grade 1. Hypotension: Immediate clinical evaluation and intervention is warranted. At the first confirmed decrease $\geq 20\%$ from baseline systolic, diastolic, or mean arterial pressure or evidence of worsening perfusion, administer an IV fluid bolus (20 mL/kg up to 1 L). Consider a vasopressor and administer no later than after the 3rd IV fluid bolus due to the vasodilation and capillary leak associated with CRS. Hypoxia: Consider X-ray or CT scan if hypoxic and/or tachypneic. Administer oxygen by low-flow nasal cannula (≤ 6 L/min) or blow-by. Tocilizumab: No* (yes, if the subject has comorbidities†). Steroids: No (consider, if the subject has comorbidities‡).
3	Fever: As per grade 1. Hypotension: Immediate clinical evaluation and intervention is warranted. Administer a vasopressor (norepinephrine), with or without vasopressin, as most patients with CRS have peripheral vasodilation. Hypoxia: Administer oxygen by high-flow nasal cannula (> 6 L/min), facemask, nonrebreather mask, or Venturi mask. Tocilizumab: Yes†. Steroids: Consider‡.
4	Fever: As per grade 1. Hypotension: Immediate clinical evaluation and intervention is warranted. Administer at least 2 vasopressors, with or without vasopressin, as most patients with CRS have peripheral vasodilation. Hypoxia: Administer positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation). Tocilizumab: Yes†. Steroids: Yes‡.

BiPAP=bilevel positive airway pressure; CNS=central nervous system; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; CT=computed tomography; IL=interleukin; IV=intravenous(ly), mAb=monoclonal antibody; NSAIDs=nonsteroidal anti-inflammatory drugs.

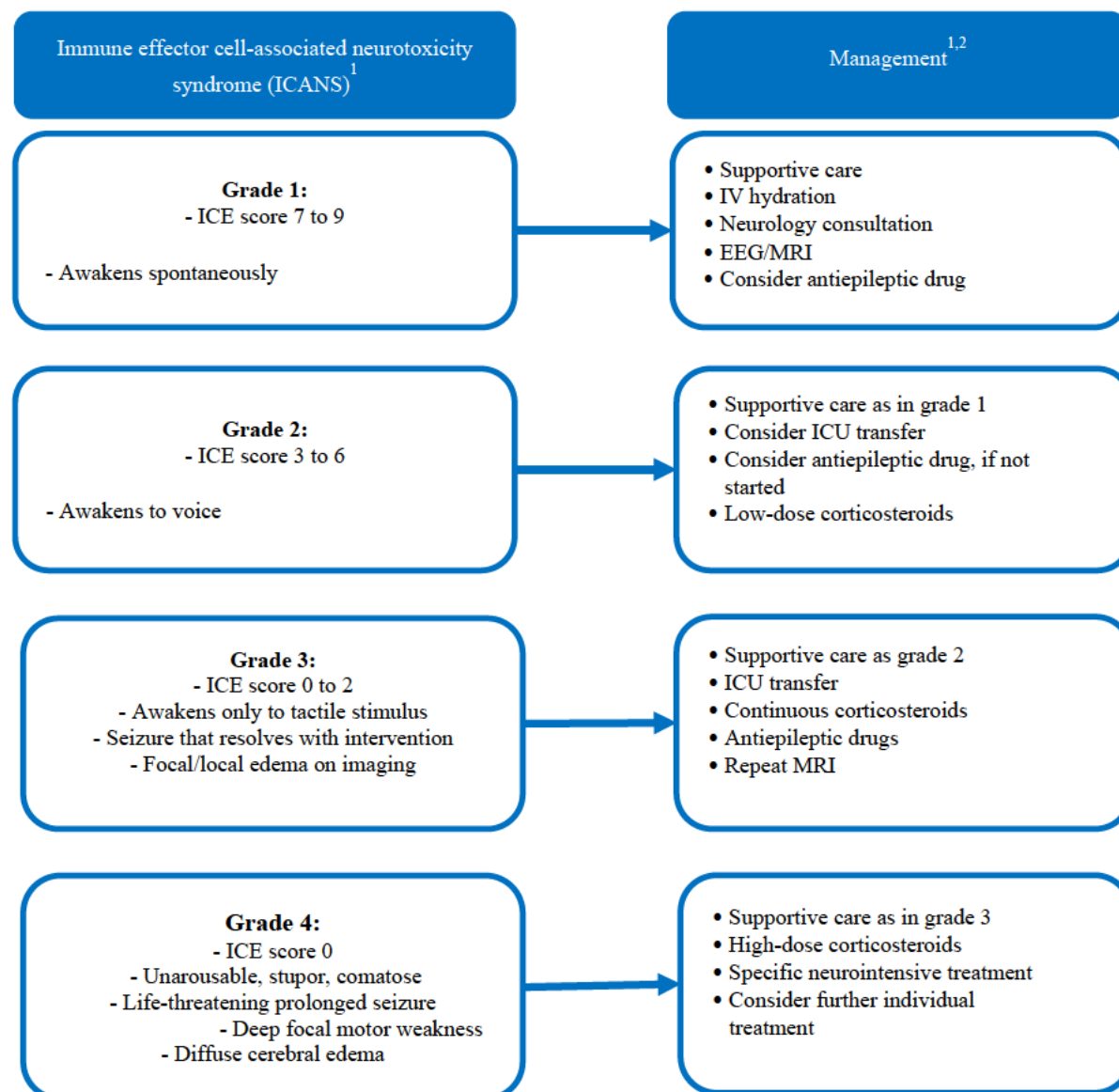
* Consider earlier intervention in specific cases. For example, an elderly subject with prolonged (> 72 hours) and/or very high (> 40.5 °C/ 104.9 °F) fever may not tolerate the resulting sinus tachycardia as well as a younger subject, so tocilizumab may be indicated.

† Tocilizumab (anti-IL-6R mAb) remains the only first-line anti-cytokine therapy approved for CRS. If there is no improvement in symptoms within 6 hours, or if the subject starts to deteriorate after initial improvement, a second dose of tocilizumab should be administered along with a dose of corticosteroids. For subjects being refractory to tocilizumab (3 administrations), additional cytokine blockade therapy such as siltuximab (anti-IL-6 mAb) or anakinra (anti-IL-1R mAb) may be considered. However, such use is anecdotal and has low level of evidence and, as such, is entirely at the discretion of the treating physician.

‡ Consider dexamethasone over methylprednisolone due to improved CNS penetration even in absence of neurotoxicity, as high-grade CRS is correlated with risk of concurrent or subsequent immune effector cell-associated neurotoxicity syndrome (ICANS). If concurrent ICANS is observed, dexamethasone should be preferred.

Source: (Varadarajan et al., 2020)

10.8 Appendix 8: Recommended ICANS Management



¹ (Lee et al., 2019).

² (Garcia Borrega et al., 2019).

EEG=electroencephalogram; ICE=Immune Effector Cell Encephalopathy; ICU=intensive care unit; IV=intravenous; MRI=magnetic resonance imaging.

10.9 Appendix 9: Supplemental Dose Modification Guidance for Standard of Care

10.9.1 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/mm³, the platelet count is $\geq 100,000$ cells/mm³.

Pemetrexed is excreted renally and it should not be administered to subjects whose CrCl is < 45 mL/min (*Note: Refer to inclusion criterion 13 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 10-2](#) and [Table 10-3](#).

Table 10-2 Pemetrexed Dose Modification Guidelines for Hematological Toxicity

Platelets μ L	ANC	Dose Level
≥ 50 AND	≥ 0.5	No reduction
≥ 50 AND	< 0.5	Reduce by 1 DL
< 50 without bleeding AND	ANY	Reduce by 1 DL
< 50 with grade ≥ 2 bleeding AND	ANY	Reduce by 2 DLs
ANY AND	< 1.0 + fever ≥ 38.5 °C (101 °F)	Reduce by 1 DL

ANC=absolute neutrophil count; DL=dose level.

Table 10-3 Pemetrexed Dose Modification Guidelines for Non-hematological Toxicity

Event	NCI-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 DLs
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

NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; DL=dose level.

The dose of pemetrexed may be reduced according to the guidelines provided below in [Table 10-4](#). 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 10-4 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

10.9.2 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. Subjects with a baseline neutrophil count $<1.5 \times 10^9/L$ or subjects with severe renal impairment (GFR <30 mL/min) should not be treated with paclitaxel.

For dose modification related to paclitaxel toxicities refer to [Table 10-5](#). 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 10-6](#).

Table 10-5 Dose Modification Guidelines for Paclitaxel

Event	Suggested Dose Modification for Toxicity
Myelotoxicity	Treatment with paclitaxel should be delayed until the absolute neutrophil count is $>1500/\mu L$ and platelet count is $>100,000/\mu L$. If a subject developed severe neutropenia ($<500/\mu L$) 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, then 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 10-6 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

10.9.3 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/mm³ should not be treated with nab-paclitaxel.

The dose of nab-paclitaxel may be reduced according to the guidelines provided below in [Table 10-7](#). 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 10-7 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

10.9.4 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 subjects. Consider alternative treatments or reduce the dose of cisplatin for injection for subjects 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 13 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. Subjects with pre-existing severe renal impairment should not receive treatment with carboplatin (*Note: Refer to inclusion criterion 13 for the trial-specific inclusion criterion for renal function*).

In EC3, 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 10-8](#).

Dose modification according to [Table 10-8](#) is allowable at the investigator's discretion for intolerable Grade 2 to 3 toxicities not specified in [Table 10-9](#) and [Table 10-10](#). 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 CRF.

Table 10-8 Dose Modification for Cisplatin and Carboplatin

Trial treatment	Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
Cisplatin ^a	75 mg/m ²	56 mg/m ² (20% decrease)	38 mg/m ² (20% decrease)	Discontinue
Carboplatin ^a	AUC 5	AUC 4 (20% decrease)	AUC 3 (20% decrease)	Discontinue
Carboplatin ^b	AUC 6	AUC 5 (20% decrease)	AUC 4 (20% decrease)	Discontinue

AUC=area under the concentration-time curve; CCI

Table 10-9 Cisplatin or Carboplatin Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

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

- a. Absolute neutrophil count <1000/mm³ ($1.0 \times 10^9/L$) and a single temperature >38.3 °C or sustained temperature ≥38 °C for >1 hour.

Table 10-10 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 ^a	Neutrophil count resolves to $\geq 1,000/mm^3$ ($1.0 \times 10^9/L$)	No reduction *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >2 DL reductions exceeded
		4 ^a	Neutrophil count resolves to $\geq 1,000/mm^3$ ($1.0 \times 10^9/L$)	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >2 DL reductions exceeded
	Thrombocytopenia	2	Platelet count resolves to $\geq 75,000/mm^3$ ($75 \times 10^9/L$) or baseline	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if >2 DL reductions exceeded
		3-4 ^a	Platelet count resolves to $\geq 75,000/mm^3$ ($75 \times 10^9/L$) or baseline	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 DL reductions exceeded
Non-hematologic	Creatinine increased	2-4 ^a	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 resolve within 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 ^b	3-4 ^a	Toxicity resolves to grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 DL reductions exceeded
	Laboratory AE ^b	4	Toxicity resolves to grade 2 or less	Reduce by 1 DL	Toxicity does not resolve within 12 weeks

					of last infusion or if >2 DL reductions exceeded
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AE=adverse event; DL=dose level; G-CSF=granulocyte colony-stimulating factor.

- a. Permanent discontinuation should be considered for any severe or life-threatening event. Consult the sponsor's medical officer before restarting treatment after grade 4 drug-related AE.
- b. Subjects with intolerable or persistent grade 2 drug-related AEs may hold at investigator's discretion. Permanently discontinue from trial treatment 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.

10.9.5 *Gemcitabine*

The most common adverse reactions for the single-agent use of gemcitabine are nausea/vomiting, anemia, increased AST, increased ALT, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and edema.

Gemcitabine will be administered at a dose of 1000 mg/m² IV over 30 minutes in combination with carboplatin AUC 2 mg/mL/min on Days 1 and 8 of each 21-day cycle (see current KEYTRUDA prescribing information for more details).

Dose modifications for gemcitabine and/or carboplatin will be implemented according to local guidelines and practices.

10.10 Appendix 10: Country-specific Considerations

10.10.1 IMP/AMP EU Authorization Status

Drug Name	IMP or AMP ^a	EU Authorization Status
GEN1055	IMP	Unauthorized
Pembrolizumab	IMP (For the dose escalation combination cohort and EC1 ^a)	Authorized
Pembrolizumab	AMP (For the expansion combination cohort)	Authorized
Pemetrexed	AMP	Authorized
Paclitaxel	AMP	Authorized
Nab-paclitaxel	AMP	Authorized
Gemcitabine	AMP	Authorized
Carboplatin	AMP	Authorized
Cisplatin	AMP	Authorized

AMP=auxiliary medicinal product; EC=expansion cohort; EU=European Union; IMP=investigational medicinal product; PD=progressive disease.

a. Only for subjects receiving GEN1055+pembrolizumab following PD on GEN1055 monotherapy.

10.10.2 Japan-specific Requirements

Management of HBV (Exclusion Criterion 13.a.)

In accordance with Japan Society of Hepatology Guidelines for the Management of Hepatitis B Virus Infection ([JSH, 2022](#)), for screening of HBV infection HBs antigen, HBs antibody and HBc antibody must be conducted. The medical history or positive serology for HBV is defined as follows,

1. HBs antigen positive
2. HBs antigen negative, HBs antibody positive and/or HBc antibody positive[#]

The subject who meets above criteria will be excluded from participating in the trial.

[#]: If HBV-DNA is negative, the subject can participate in the trial with conducting the tests of HBV-DNA and AST/ALT regularly (every 1 to 3 months after trial treatment initiation).

Definition of Reproductive Potential and Contraception

In this trial, a female is considered of childbearing 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 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.

Female subjects of reproductive potential must agree to use adequate contraception during the trial treatment and for 6 months after the last dose of GEN1055. Adequate contraception is defined as highly effective methods of contraception (Table 10-11). 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 10-11 Highly Effective Methods of Contraception – Trials Conducted in Japan

- | |
|--|
| <ul style="list-style-type: none"> • Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: <ul style="list-style-type: none"> ○ Oral • Intrauterine device^a • Intrauterine hormone-releasing system^a • Bilateral tubal occlusion^a • Vasectomized partner^{a,b} • Sexual abstinence^c |
|--|

Adapted from “Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1.” (CTFG, 2020).

- a. Contraception methods that in the context of this guidance are considered to have low user dependency.
- b. Vasectomized partner is a highly effective birth control method, provided that partner is the sole sexual partner of the female of child-bearing potential trial subject, and that the vasectomized partner has received medical assessment of the surgical success.
- c. 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 treatment. The reliability of ‘not engaging in sexual intercourse’ needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Other Japan-specific Requirements

Japanese country-specific language is shown in **bold text**.

Section	Country-Specific Language
5.1 Inclusion Criteria	10. A male subject who is sexually active with a female with reproductive 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 GEN1055 administration; all males must also refrain from donating sperm during the trial and for 6 months after receiving the last dose of GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice. Spermicidal foam/gel/film/cream/suppository are not available in Japan.
6.1 Investigational and Auxiliary Medicinal Products Table 6-2 Auxiliary Medicinal Product(s)	Pembrolizumab, Pemetrexed, Paclitaxel, Nab-paclitaxel, Gemcitabine, Cisplatin and Carboplatin are used as “Drugs used in the Clinical Trial other than test drugs”
6.4.2 Drug Accountability and Destruction	The head of the trial site has overall responsibility for the trial drug. Tasks will be delegated to a qualified designee (eg, the trial drug manager) who is adequately trained in the protocol. This delegation must be documented in the applicable trial delegation of an authority form.

	The trial drug will not be dispatched to the trial site until the sponsor or designee has received all required documents from the trial site in accordance with relevant standard operating procedures. Upon receipt, the designee (the trial drug manager) who is assigned by the head of the trial site is responsible for ensuring that all trial drugs received at the trial site is inventoried and accounted for throughout the trial. A copy of the shipping documents must be maintained for the investigator's records. After sufficient amount of the trial drug is shipped to the trial site, the designee (the trial drug manager) will acknowledge receipt of the trial drug, documenting shipment content and condition. Accurate records of all trial drug dispensed, used and/or destroyed must be maintained as detailed later in this section. A qualified designee for the trial drug (the trial drug manager) will supply the trial drug only to the investigator or staff in this trial who administers to the subject according to procedures set out in the trial protocol. The designee (the trial drug manager) should keep a current record of the inventory and dispensing of all clinical supplies. All administered/dispensed trial drug will be documented in the subject's source and/or other trial drug records. The designee (the trial drug manager) is also responsible for ensuring the retrieval of all trial supplies from subjects. Further guidance and information for the final disposition of unused trial drug or return after use are provided in the administration and preparation guideline for additional guidance on trial drug preparation, handling, and storage. The sponsor or its representatives will be permitted access to review the supplies storage, distribution and their records anytime.
8.4.4 Regulatory Reporting Requirements	The sponsor will ensure that all relevant information about SUSARs is documented and reported as soon as possible, but within a maximum of 15 calendar days (fatal or life-threatening SUSARs within a maximum of 7 calendar 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 within the required reporting timelines. The sponsor will also communicate relevant information on SUSARs with the investigators and the head of the trial site and IEC/IRB in predefined periods and according to local regulations.
10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations	The principles of the Declaration of Helsinki, standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the "Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices", Ministerial Ordinance on Good Clinical Practice for Drugs Ordinance of the Ministry of Health and Welfare (J-GCP), 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. Generally, the priority is given to J-GCP for definitions of terminology and other minor differences between J-GCP and ICH GCP.
10.1.3 Independent Ethics Committee or Institutional Review Board	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 head of the trial site. The head of the trial site will submit them to the IEC/IRB for review and written 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 noncompliance, 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 review(s) of trial progress will be submitted by the investigator, where applicable, to head of the trial site, and then, the head of the trial site will seek the opinion of the IEC/IRB with respect to the appropriateness of continuing the trial at the trial site at least once a year when the duration of the clinical trial exceeds 1 year.

	At the end of the trial, the investigator (or sponsor where required) will notify the head of the trial site about the trial completion, and the head of the trial site will notify the IEC/IRB and the sponsor.
10.1.5.2 Regulatory Documentation	This protocol and any amendments where necessary , 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.
10.1.7 Data Protection	The head of trial site will ensure that the confidentiality of all 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 ICF will be maintained by the investigator in strict confidence.
10.1.10.2 Record Retention	In compliance with current J-GCP , ICH GCP E6(R2), the investigator/institution/ IRB/sponsor 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 Record Retention of Article 26, 34 and 41 of J-GCP, and 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/ IRB 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/ IRB as to when these documents no longer need to be retained. Medical Records (subjects' hospital record) is retained/archived according to applicable local regulation.
10.1.10.3 Monitoring	The head of the trial site and the investigator must permit the monitor access to all source data, including electronic medical records, and/or documents with the purpose of verifying that the data recorded in the eCRF are consistent with the original source data.
10.3 Appendix 3: Definition of Reproductive Potential and Contraception	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 the trial and for 6 months after the last GEN1055 administration; all men must also refrain from donating sperm during the trial and for 6 months after receiving the last dose of GEN1055. For pembrolizumab and chemotherapy, please refer to the respective prescribing information or SoC per local practice. Spermicidal foam/gel/film/cream/suppository are not available in Japan.

10.10.3 France-specific Requirements

France country-specific requirements are shown below.

Section	Country-Specific Language
5.2, Exclusion Criterion 11	The following exclusion criteria apply in France: • Persons deprived of liberty by judicial or administrative decision. • Persons subject to forced psychiatric care. • Persons of full age who are subject to a legal protection measure (under guardianship or curatorship). • Persons under a legal protection measure. • Persons who are not affiliated with a social security or equivalent plan.

11 LAY PROTOCOL SYNOPSIS

Protocol Title	First-In-Human, Open-Label, Dose Escalation Trial with Expansion Cohorts to Evaluate the Safety and Preliminary Efficacy of GEN1055 as Monotherapy and as Combination Therapy in Subjects With Malignant Solid Tumors.	
Brief Title	Trial to assess the safety and preliminary efficacy of GEN1055 on malignant solid tumors as monotherapy and as combination therapy.	
Protocol Number	GCT1055-01	
Regulatory Agency Identifier Number(s)	EU CT No.	2023-507049-28-00
	NCT No.	Not available
Brief Summary The goal of this trial is to learn about the antibody GEN1055 when it is used alone and when it is used together with another antibody cancer drug, pembrolizumab (with or without chemotherapy), for treatment of patients with certain types of cancer. Subjects will receive either GEN1055 alone, GEN1055 with pembrolizumab, or GEN1055 with pembrolizumab and chemotherapy. All participants 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 GEN1055 is safe and to find out the best doses of GEN1055 to use alone and to use with pembrolizumab. The purpose of the second part is to give GEN1055 to more patients to see how well the doses of GEN1055 that were selected in the first part work against cancer alone and how well they work with pembrolizumab (with or without other chemotherapy). A subject will receive trial treatment up to a maximum of 24 months for pembrolizumab-containing regimens, or until: - the cancer progresses. - there are side effects requiring that treatment be stopped. - the subject decides to withdraw. - the doctor believes it is in the subject's best interest to stop treatment. Participation in the trial will require visits to the site. For the first 12 weeks there will be weekly visits and after that, visits will be every 3 weeks. At site visits, there will be various tests (such as blood draws) and procedures (such as recording of heart activity, CT scans) to monitor whether the treatment is safe and effective. The trial duration (including screening, treatment, and follow-up) for each participant will be about 39 months.		
Rationale GEN1055, also known as HexaBody-OX40, is an antibody that belongs to a group of drugs known as immunotherapy. It binds to a molecule on cells involved in killing cancer cells. Studies in animals have shown that GEN1055 can stimulate the fighting of cancer by binding to these cells. GEN1055 may not only work alone but also together with other cancer drugs. In this trial, GEN1055 will be tested in humans for the first time.		
Objectives/Endpoints		
Part 1		
Primary Objective(s)	Primary Endpoint(s)	
Determine if GEN1055 is safe when given alone or when given with pembrolizumab	- How often side effects occur and how serious they are - How often laboratory values are outside the normal range and by how much	
Determine the dose of GEN1055 to be used alone and to be used with pembrolizumab in the second part of the trial	How often "dose-limiting toxicities," which are a specific type of side effects that guide investigators about what doses to test next, occur	

<i>Secondary Objective(s)</i>	<i>Secondary Endpoints(s)</i>
Evaluate how the body handles GEN1055 when GEN1055 is given alone and when it is given with pembrolizumab	Amount of GEN1055 in the blood and how the amount changes over time
Evaluate if the body reacts to GEN1055	Amount of an antibody in the blood that could react to GEN1055
Evaluate how the tumor is affected by GEN1055 when given alone or when given with pembrolizumab	The following will be determined using scans done throughout the trial: • Objective response rate (a measurement of how the tumor has reacted [gotten smaller or larger] to treatment) • Duration of response (the time period with tumor shrinkage before the growth starts again) • Time to response (the time period before the tumor stops growing and/or tumor shrinkage can be measured) • Disease control rate (the percentage of subjects who obtained either tumor shrinkage or stopping of the tumor growth during the treatment)
<i>Part 2</i>	
<i>Primary Objective(s)</i>	<i>Primary Endpoint(s)</i>
Evaluate how the tumor is affected by GEN1055 when given alone or when given with pembrolizumab	Objective response rate will be determined using scans done throughout the trial
<i>Secondary Objective(s)</i>	<i>Secondary Endpoint(s)</i>
Evaluate how the tumor is affected by GEN1055 when given alone or when given with pembrolizumab	The following will be determined using scans done throughout the trial: • Duration of response • Time to response • Progression-free survival (how long it takes for subjects with tumor shrinkage before their tumor starts to grow again) • Disease control rate Also, how long a subject lives after the first dose of GEN1055 will be measured.
Determine if GEN1055 is safe when given alone or when given together with pembrolizumab	• How often side effects occur and how serious they are • How often laboratory values are outside the normal range and by how much
Evaluate how the body handles GEN1055 when GEN1055 is given alone and when it is given with pembrolizumab	Amount of GEN1055 in the blood and how the amount changes over time
Evaluate if the body reacts to GEN1055	Amount of an antibody in the blood that could react to GEN1055
Trial Population In Part 1: Patients with various cancers for which there is no available treatment, 18 years of age or older. In Part 2: Patients with cancers CCI 18 years of age or older.	
Intervention GEN1055 and pembrolizumab will be injected into a vein once every 3 weeks. Chemotherapy drugs will also be injected into a vein. Some chemotherapy drugs are given every 3 weeks and others are given weekly.	

Ethical Considerations

Research in cells and animals suggests that GEN1055 may be effective in treating cancer in humans and may also work together with other cancer drugs, such as pembrolizumab. Pembrolizumab is approved for the treatment of patients with various cancer types, including those of the CCI [REDACTED]. However, GEN1055 has not been tested in humans yet.

Being treated with GEN1055 alone or in together with pembrolizumab in this trial may or may not make the health better for an individual subject. Although the health of 1 subject may not get better, other subjects may benefit from the knowledge gained from this trial in the future. Subjects' health will be observed and monitored during the trial and all tests and procedures performed throughout the trial are done to find out if GEN1055 given alone or given with pembrolizumab is both safe and effective (that is, the drugs can fight cancer).

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Protocol Amendment Summary of Changes

Protocol Amendment 3 (12-Feb-2025)

Overall Rationale for the Amendment:

This amendment was prepared as an Urgent Safety Measure to mitigate the risk of IRR and to address feedback received from FDA.

Description of Changes:

Section	Description of Change	Brief Rationale
Section 6.8.1 Dose-Limiting Toxicity	Update criteria such that all IRR $\geq$ grade 3 are considered DLTs	Per FDA request
Section 6.8.3.3 Infusion-Related Reactions Associated With GEN1055 Administration	Prior to each dose of GEN1055, all subjects should be premedicated with diphenhydramine at 50 mg (or an equivalent antihistamine) and acetaminophen/paracetamol at 1 g	Mitigate risk of IRR