CLINICAL TRIAL PROTOCOL

Protocol Title	First-in-Human, Open-label, Dose-Escalation Trial with Expansion Cohorts to Evaluate the Safety of GEN1053 as Monotherapy and in Combination With an Immunomodulator in Subjects with Malignant Solid Tumors	
Protocol Number	GCT1053-01	
Compound	GEN1053	
Brief Title	A Study to Evaluate Safety, Tolerability, and Preliminary Effect of the GEN1053 Antibody on Malignant Solid Tumors as Monotherapy and in Combination.	
Trial Phase	Phase 1/2a	
Sponsor Name	Genmab*	
Collaborator Name	BioNTech	
Regulatory Agency Identifier Numbers	EU CT No.	2022-502419-12-00
	NCT No.	NCT05435339
	IND No.	160884
Protocol Approver**	Name	PPD , MD, PhD
	Title	PPD
Protocol Version History	Version	Document Date
	Original Protocol, v1.0	06 Apr 2022
	Protocol Amendment 1, v2.0	29 Aug 2022
	Protocol Amendment 1_EU-1, v1.0	07 May 2024

* Genmab is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Genmab trials may vary, such as, but not limited to Genmab Holding B.V.; Genmab B.V.; Genmab A/S; or Genmab US, Inc. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the following sponsor information page.
** This protocol was approved via electronic signature on the approval page appended to the document.

CONFIDENTIALITY STATEMENT

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied that is indicated as privileged or confidential.

SPONSOR INFORMATION PAGE

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

The sponsor contact information page will be provided separately; listing the trial responsible medical director, as well as the CRO(s), laboratory(ies) (names and addresses), and other technical/medical services used. Additional contact information may be found in the trial specific manuals (eg, IMP Manual, Laboratory Manual).

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, 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.

Coordinating Investigator (where required):	
Name (typed or printed):	
Institution and Address:	

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

Note: If the address or telephone number of the investigator changes during the course of the trial, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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

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STATEMENT OF COMPLIANCE

GCP Compliance

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

Confidentiality Statement

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1 PROTOCOL SUMMARY

1.1 Trial Synopsis

Title	First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate the safety of GEN1053 as monotherapy and in combination with an immunomodulator in subjects with malignant solid tumors	
Short Title	A study to evaluate safety, tolerability, and preliminary effect of the GEN1053 antibody on malignant solid tumors as monotherapy and in combination.	
Indication	Solid tumors, head and neck squamous cell carcinoma (HNSCC), non–small cell lung cancer (NSCLC)	
Clinical Phase	Phase 1/2a	
Purpose and Rationale	GEN1053 is an agonistic CD27 antibody designed to (re)activate and increase antitumor immunity through induction of costimulatory signaling by Fc gamma receptor (FcγR)-independent CD27 clustering on the surface of activated T cells. Combination strategies to improve GEN1053 activity and antitumor responses may be achieved by combining with an immunomodulator (IM) CCI [redacted] The aim of this first-in-human (FIH) trial for GEN1053 is to investigate safety, establish the maximum tolerated dose (MTD) and/or maximum administered dose (MAD), and determine the recommended phase 2 doses (RP2Ds) of GEN1053 monotherapy and GEN1053+IM combination therapy in a sequential dose escalation setting. A subsequent Expansion part will further evaluate safety and serve to establish a preliminary assessment of efficacy in selected indications.	
Objectives and Endpoints	**OBJECTIVES**	**ENDPOINTS**
	Primary	
	• Determine MTD/MAD/RP2Ds of GEN1053 as monotherapy and in combination with IM • Establish initial safety profile of GEN1053 as monotherapy and in combination with IM	• Dose-limiting toxicities (DLTs; Dose Escalation parts only) • Adverse events (AEs) and safety laboratory parameters
	Secondary	
	• Establish pharmacokinetic (PK) profile of GEN1053 as monotherapy and in combination with IM	• PK parameters for GEN1053: clearance [CL], volume of distribution [V], maximum concentration [C_{max}], time of C_{max} [t_{max}], predose trough concentrations [C_{trough}], half-life [$t_{1/2}$], area under the concentration-time curve [AUC_{last} and AUC_{tau}]
	• Evaluate immunogenicity of GEN1053 as monotherapy and in combination with IM	• Antidrug antibody response of GEN1053 and in combination with IM
	• Evaluate antitumor activity of GEN1053 as monotherapy and in combination with IM	Antitumor activity according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1: • Objective response rate (ORR) • Disease control rate (DCR) • Duration of response (DoR)

Trial Design and Duration	This is an FIH phase 1/2a open-label, multicenter, multinational trial in subjects with non–central nervous system (non-CNS) metastatic or advanced malignant solid tumors for whom there is no available standard therapy likely to confer clinical benefit, evaluating the safety, tolerability, preliminary antitumor activity, PK, pharmacodynamics, and immunogenicity of GEN1053 as monotherapy and in combination with IM. The trial will be conducted as follows: • The Dose Escalation part will explore the safety of escalating doses of GEN1053 as monotherapy (phase 1a) as well as escalating doses of GEN1053 when combined with a fixed dose of an IM (phase 1b) in a sequential approach in a population of subjects with various solid tumors. • The Expansion part is planned to provide additional safety and initial antitumor activity information of the RP2Ds for GEN1053 monotherapy and GEN1053+IM combination therapy, respectively, in selected tumor indications, as well as more detailed data related to the mode of action (MoA) (monotherapy), sequencing (crossover from monotherapy to IM combination therapy upon PD, as applicable) and combination with IM. Each part will consist of a screening period (up to 21 days prior to Cycle 1 Day 1 [C1D1]), a treatment period (C1D1 until discontinuation of trial treatment, and 2 safety follow-up visits 30 days and 60 days after the last dose of trial treatment, preceding the survival follow-up. Subjects will be treated in cohorts, defined as a group of subjects allocated to the same treatment. Both GEN1053 and IM will per default be administered as an IV infusion in 3-week (ie, 21-day) cycles (Q3W) until PD, unacceptable AE, or withdrawal of consent. A trial-independent data monitoring committee (DMC), a safety committee (SC), and a dose escalation committee (DEC) will be commissioned for this trial. During the Dose Escalation part, DLTs will be assessed in the first treatment cycle at each dose level (DL). The DEC will assess all available data with focus on safety and make recommendations for the next DL and propose the RP2D/MTD/MAD to the DMC and SC. The SC will make the final decisions.
Population and Sample Size	The multicenter, multinational trial population includes male and female subjects who are ≥18 years of age, with malignant non-CNS solid tumors. This trial is projected to enroll approximately 170 subjects as follows: • In the Monotherapy Dose Escalation phase 1a: up to 63 (maximum 9 subjects at each DL) • In the Combination therapy Dose Escalation phase 1b: up to 27 subjects (maximum 9 subjects at each DL) • In the Expansion part: approximately 80 subjects (approximately 40 subjects for each cohort)
Key Inclusion Criteria	**For both the Dose Escalation and Expansion parts** Subject must: • Be ≥18 years of age. • Have measurable disease according to RECIST 1.1. • Provide all prebaseline scans since failure of last prior therapy (ie, documented radiographic PD), if available. • Have Eastern Cooperative Oncology Group performance status ≤1. • Have organ and bone marrow function as follows: ○ Bone marrow/hematological function: ▪ Absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L ▪ Hemoglobin ≥9.0 g/dL ▪ Platelet count $\geq 150\times10^9$/L ○ Liver function: ▪ Total bilirubin ≤ upper limit of normal (ULN) ▪ Alanine aminotransferase ≤1.5×ULN

	▪ Aspartate aminotransferase ≤1.5×ULN ▪ Albumin ≥30 g/L ○ Coagulation status: ▪ Prothrombin time (PT)/International normalized ratio ≤1.5 ▪ Activated partial thromboplastin time (aPTT) ≤1.5×ULN ○ Renal function: Glomerular filtration rate ≥45 mL/min/1.73 m², according to the abbreviated Modification of Diet in Renal Disease equation **For Monotherapy Dose Escalation (phase 1a) and Combination therapy Dose Escalation (phase 1b) only:** • Subjects with histologically or cytologically confirmed non-CNS solid tumors that are metastatic or advanced. • Subjects who have progressed on standard of care therapy or for whom there is no available standard therapy likely to provide clinical benefit, or who are not candidates for available therapy or who have previously refused available therapy, and for whom experimental therapy with GEN1053 or GEN1053+IM may be beneficial, in the opinion of the investigator. • Biopsies for Monotherapy Dose Escalation and Combination therapy Dose Escalation: ○ All subjects must provide a fresh biopsy. A fresh biopsy is defined as being taken after failure/stop of last prior treatment and within 6 months prior to C1D1. *Note: Documentation of fresh 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.* **For the Expansion part Only:** • Subjects with histologically or cytologically confirmed diagnosis of recurrent, unresectable, or metastatic HNSCC or metastatic NSCLC, who do not have any further available standard therapy or who are not candidates for standard therapy or who have previously refused standard therapy (if subjects had access), and for whom experimental therapy with GEN1053 (HNSCC) or GEN1053+IM (NSCLC, HNSCC crossover) may be beneficial, in the opinion of the investigator. • Subjects must meet the following criteria in the respective Expansion cohorts: **For Expansion Cohort 1 (MoA cohort, HNSCC) GEN1053 with crossover to GEN1053+IM:** ○ Subjects with recurrent, unresectable, or metastatic HNSCC (with no surgery or RT options) of the oral cavity, pharynx, or larynx who have received up to 3 prior systemic treatment regimens for recurrent/metastatic disease with radiographic PD on or after last prior treatment (maintenance treatment is considered part of one treatment line). ○ Subjects must have received prior platinum-based therapy or alternative chemotherapy if platinum ineligible (eg, a gemcitabine-containing regimen). ○ Subjects must have received 1 prior treatment with a PD-1/PD-L1 inhibitor alone or in combination with other therapy and must have had radiographic PD on or within 6 months after treatment. *Note: For the subjects whose most recent anticancer therapy contained a PD-1/PD-L1 inhibitor, their recent evidence of PD must be confirmed by a second radiographic assessment at least 4 weeks from the date of the initial radiologically documented PD.* ○ Biopsies for Expansion Cohort 1:

	▪ All subjects must provide a fresh biopsy. A fresh biopsy is defined as being taken after failure/stop of last prior treatment and within 6 months prior to C1D1. *Note: Documentation of fresh 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 .* **For Expansion Cohort 2 (NSCLC) GEN1053+IM:** ○ Subjects with metastatic NSCLC who have received up to 4 prior systemic treatment regimens for advanced/metastatic disease with radiographic PD on or after last prior treatment (maintenance treatment is considered being part of 1 treatment line). ▪ NSCLC tumors of any histology may be enrolled. Subjects with mutations in KRAS, BRAF, MET genes or RET gene rearrangements or NTRK1/2/3 gene fusions in their tumors may only be enrolled after prior treatment with targeted therapy/standard of care options. Subjects with drug-sensitizing mutations in EGFR or ALK or ROS1 rearrangements are not eligible. Documentation of genomic status should be available per local assessment. *Note: For subjects with squamous NSCLC histology, molecular testing for genomic alterations will not be required.* ○ Subjects must have received prior platinum-based therapy or alternative chemotherapy if platinum ineligible (eg, a gemcitabine-containing regimen). ○ Subjects must have received 1 prior treatment with a PD-1/PD-L1 inhibitor alone or in combination with other therapy and must have had radiographic PD on or within 6 months after treatment. *Note: For the subjects whose most recent anticancer therapy contained a PD-1/PD-L1 inhibitor, their recent evidence of PD must be confirmed by a second radiographic assessment at least 4 weeks from the date of the initial radiologically documented PD.* ○ Biopsies for Expansion Cohort 2: ▪ All subjects must provide a fresh biopsy. A fresh biopsy is defined as being taken after failure/stop of last prior treatment and within 6 months prior to C1D1. *Note: Documentation of fresh 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.*
Key Exclusion Criteria	• Has uncontrolled intercurrent illness, including but not limited to: ○ Ongoing or active infection requiring IV treatment with anti-infective therapy administered less than 2 weeks prior to first dose. ○ Symptomatic congestive heart failure (Grade III or IV as classified by the New York Heart Association), unstable angina pectoris, or cardiac arrhythmia. ○ Uncontrolled hypertension defined as systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg, despite optimal medical management. ○ Prolonged QTc 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 irAEs. ○ 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. ○ History of chronic liver disease or evidence of hepatic cirrhosis. ○ Evidence of interstitial lung disease. ○ Ongoing pneumonitis or history of noninfectious pneumonitis that has required steroids. ○ Known platelet function defects or a known history or high risk of bleeding events requiring transfusions or hospitalizations unless approved by sponsor.

	• Any subject with history of intracerebral arteriovenous malformation (shunts), cerebral aneurysm, spinal cord compression (from disease), carcinomatous meningitis, or stroke will be excluded. ○ Transient ischemic attack >1 month prior to screening is allowed. ○ Subjects with newly identified or known unstable or symptomatic CNS metastases will be excluded. Subjects with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of 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). • Prior therapy: ○ Radiotherapy within 14 days prior to first trial treatment administration. Palliative radiotherapy will be allowed. ○ Treatment with an anticancer agent (within 28 days or after at least 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 (G-CSF/GM-CSF) support within 2 weeks prior to first trial treatment administration or is chronically transfusion dependent. • Known history/positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy): ○ Positive test for antibodies to hepatitis B core antigens **and** ○ Negative test for antibodies to hepatitis B surface antigens. • Known medical history or ongoing hepatitis C infection that has not been cured. • Prior treatment with an anti-PD-1/PD-L1 targeting agent within 6 months prior to the initiation of trial treatment.
Trial Treatments	GEN1053 as monotherapy and in combination with an IM will be administered IV Q3W.
Other Trial Treatment	N/A
Efficacy Assessments	• Radiological/imaging assessments • Survival status
Safety Assessments	• Adverse events • Clinical laboratory assessments • Physical examinations • Vital signs • 12-lead electrocardiograms (ECGs) • Eastern Cooperative Oncology Group performance status (ECOG-PS)
Other Assessments	• PK and immunogenicity samples • Biomarkers from blood and biopsy samples
Statistics	For the Dose Escalation part, no formal sample size calculation was performed. The Dose Escalation part will enroll subjects from a range of cancer types. In phase 1a, a Bayesian logistic regression model (BLRM) will be used to guide the choice of GEN1053 monotherapy dose. In phase 1b, the choice of an optimal combination dose will be guided by Bayesian optimal interval method (BOIN), with a flat DL of IM, but could potentially consider different DLs of IM. For the Expansion part, no formal sample size calculation has

	been conducted, but 40 subjects would ensure at least 90% power to detect a shift to an ORR of 30% from a base rate of 10% given a 1-sided binomial test at a 5% significance level. A futility analysis will be conducted after 10 and/or 20 subjects to estimate the predictive probability of success. The probability of success estimate will be updated as data accumulates.
GCP Compliance	This trial will be conducted in compliance with the principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice ICH GCP E6(R2), and applicable regulatory requirements.

1.2 Schema

Figure 1-1 Schematic Overview of the Trial

1.3 Schedule of Activities

Table 1-1 through Table 1-19 list all assessments and indicate with an "X" the evaluations performed by visit. In addition to the planned visits, it may be necessary to perform some of the assessments at unscheduled time points if deemed clinically necessary by the investigator.

Table Number	Table Title
Dose Escalation	
Table 1-1	Schedule of Activities – Dose Escalation – GEN1053 Monotherapy
Table 1-2	PK, ADA, and ECG Sampling – Dose Escalation – GEN1053 Monotherapy
Table 1-3	Biomarker Evaluation Schedule – Dose Escalation – GEN1053 Monotherapy
Table 1-4	Vital Signs – Dose Escalation – GEN1053 Monotherapy
Table 1-5	Schedule of Activities – Dose Escalation – GEN1053+IM Combination Therapy
Table 1-6	PK, ADA, and ECG Sampling – Dose Escalation – GEN1053+IM Combination Therapy
Table 1-7	Biomarker Evaluation Schedule – Dose Escalation – GEN1053+IM Combination Therapy
Table 1-8	Vital Signs – Dose Escalation – GEN1053+IM Combination Therapy
Expansion	
Table 1-9	Schedule of Activities – Expansion – Subjects With HNSCC – GEN1053 Monotherapy
Table 1-10	PK and ADA Sampling – Expansion – Subjects With HNSCC – GEN1053 Monotherapy
Table 1-11	Biomarker Evaluation Schedule – Expansion – Subjects With HNSCC – GEN1053 Monotherapy
Table 1-12	Vital Signs – Expansion – Subjects With HNSCC – GEN1053 Monotherapy
Table 1-13	Schedule of Activities – Expansion – Crossover Subjects With HNSCC – GEN1053+IM Combination Therapy
Table 1-14	Schedule of Activities – Expansion – Subjects With NSCLC – GEN1053+IM Combination Therapy
Table 1-15	PK and ADA Sampling – Expansion – Crossover Subjects With HNSCC – GEN1053+IM Combination Therapy
Table 1-16	PK and ADA Sampling – Expansion – Subjects With NSCLC – GEN1053+IM Combination Therapy
Table 1-17	Biomarker Evaluation Schedule – Expansion – Crossover Subjects With HNSCC – GEN1053+IM Combination Therapy
Table 1-18	Biomarker Evaluation Schedule – Expansion – Subjects With NSCLC – GEN1053+IM Combination Therapy
Table 1-19	Vital Signs – Expansion – Subjects With NSCLC and Crossover Subjects With HNSCC – GEN1053+IM Combination Therapy

1.3.1 Dose Escalation (Monotherapy)

Table 1-1 Schedule of Activities – Dose Escalation – GEN1053 Monotherapy

Cycle /Visit	Protocol Section	Screening	Cycles 1-2				Cycles 3-4			Cycles 5 to X	Treatment Discon-tinuation	SFU1	SFU2	Survival Follow-up	UNS
Day		**≤21 days prior to Visit C1 (D1)**	**D1**	**D3**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	-	**30 days after last dose of trial treatment**	**60 days after last dose of trial treatment**	**Every 12 weeks after last dose of trial treatment[a]**	
Visit Window			**+3d[c]**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	-	**+5d**	**±7d**	**±14d**	
Informed consent	Appendix 1	X[b]													
Eligibility criteria	5	X													
Demographics	8.1.1	X													
Diagnosis and disease status	8.1.2	X													
Medical history	8.1.3	X													
Height	8.3.2.1	X													
Body weight	8.3.2.2	X	X				X			X	X				
Physical examination	8.3.1	X	X		X[e]	X[e]	X	X[e]	X[e]	X	X	X			X[d]
Vital signs[f]	8.3.3, Table 1-4	X	X		X	X	X	X[e]	X[e]	X	X	X			X[d]
ECG	8.3.4	X	See Table 1-2 and Section 8.3.4												
CT/MRI scan	8.2	X	See Section 8.2												
Prebaseline imaging scans and labs	8.2.3, 8.3.6	X													
ECOG PS	8.3.5	X	X				X			X	X	X			X[d]
Adverse events	8.4, 8.4.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]
Prior and concomitant medications	6.6	X	X	X	X	X	X	X	X	X	X	X	X		X[d]
GEN1053 administration[g]	6		X				X			X					
End of treatment	7										X				
New anticancer treatment	7.1.1										X	X	X	X	
Survival follow-up	7.1.2													X	
LOCAL LABORATORY ASSESSMENTS															

Cycle /Visit	Protocol Section	Screening	Cycles 1-2				Cycles 3-4			Cycles 5 to X	Treatment Discon-tinuation	SFU1	SFU2	Survival Follow-up	UNS
Day		**≤21 days prior to Visit C1 (D1)**	**D1**	**D3**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	-	**30 days after last dose of trial treatment**	**60 days after last dose of trial treatment**	**Every 12 weeks after last dose of trial treatment[a]**	
Visit Window			**+3d[c]**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	-	**+5d**	**±7d**	**±14d**	
Hematology	8.3.6, Table 10-1	X[h]	X[i]	X	X	X	X[i]	X	X	X[i]	X	X	X		X[d]
Biochemistry	8.3.6, Table 10-1	X[h]	X[i]	X	X	X	X[i]	X	X	X[i]	X	X	X		X[d]
Coagulation factors	8.3.6, Table 10-1	X[h]	X[i]	X	X	X	X[i]	X	X	X[i]	X	X	X		X[d]
Endocrine	8.3.6, Table 10-1	X[h]	X[i]				X[i]			X[i]	X				X[d]
Urinalysis	8.3.6, Table 10-1	X[h]	X[i]				X[i]			X[i]	X	X	X		X[d]
Pregnancy test	8.3.6, Table 10-1	X[h]	X[i]				X[i]			X[i]	X	X	X		X[d]
Hepatitis B	8.3.6, Table 10-1	X[h]									X				X[d]
CENTRAL LABORATORY ASSESSMENTS															
PK/ADA sampling	8.5	See Table 1-2													
Biomarkers	8.7	See Table 1-3													

ADA= antidrug antibody; C=cycle; CT=computed tomography; d=D/day(s); ECG= electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; MRI=magnetic resonance imaging; PK= pharmacokinetic(s); SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.

a. For the last subject discontinuing treatment, there will be no survival follow-up and the last visit for that subject will be SFU 2.
b. Informed consent must be obtained prior to the screening period.
c. Visit window (+3d) applies to Cycle 2 Day 1 only.
d. Optional.
e. A physical examination and vital signs should only be performed as indicated by the subject's symptoms, adverse events, or other findings as determined by the investigator.
f. Temperature, blood pressure, and heart rate should be measured according to Table 1-4 on infusion days. On noninfusion days, vital signs should be obtained any time during the visit.
g. Refer to Section 6.7.2.3 for details on post GEN1053 infusion precautions and observation periods.
h. All local laboratory samples at the screening visit must be obtained within 7 days prior to Cycle 1 Day 1 (with the exception of hepatitis B sample, which may be obtained earlier).
i. Local laboratory samples should be obtained on Day 1 of each cycle or no more than 3 days before the visit for Cycle 2 and beyond and reviewed before dosing.

Table 1-2 PK, ADA, and ECG Sampling – Dose Escalation – GEN1053 Monotherapy

Cycle/Visit	Screening	Cycle 1				Cycle 2	Cycle 3			Cycles 4 to X	Treatment Discontinuation	SFU1	SFU2	UNS
Day	≤21 days prior to Visit C1 (D1)	D1	D3	D8	D15	D1	D1	D8	D15	D1[c]	-	30 days after last dose of trial treatment	60 days after last dose of trial treatment	-
Visit Window			+2d	±1d	±1d	+3d	±3d	±1d	±1d	±3d		+5d	±7d	
PK Sampling (Section 8.5)														
Preinfusion (on infusion days)		X				X	X			X	X	X	X	X[b]
EOI + 5 min (+ 5 min)		X				X	X			X				
EOI + 2 hr (± 30 min)		X					X							
EOI + 4 hr (± 1 hr)		X												
EOI + 48 hr (+ 2 days)			X											
EOI + 168 hr (± 1 day)				X				X						
EOI + 336 hr (± 1 day)					X				X					
ADA Sampling (Section 8.8)														
Preinfusion (on infusion days)		X				X	X			X[a]	X	X	X	X[b]
ECG[c] (Section 8.3.4)														
Preinfusion (on infusion days)	X	X				X	X			X	X	X	X	X[b]
EOI (+ 15 min)		X				X								
EOI + 2 hr (±15 min)		X				X	X			X				

ADA=antidrug antibody; C=cycle; ECG=electrocardiogram; D/d=day(s); EOI=end of infusion; hr=hours; min=minutes; PK=pharmacokinetic(s); SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.

Note: Clock time must be recorded for infusion start and stop, and for each sample collected.

a. ADA sample at even-numbered cycles only.

b. Optional.

c. ECGs are to be taken as single assessments. From Cycle 5, ECGs must be obtained at Cycle 5, Cycle 7, and every 4 cycles thereafter (ie, Cycles 11, 15, etc.)

Table 1-3 Biomarker Evaluation Schedule – Dose Escalation – GEN1053 Monotherapy

Cycle/Visit[a]	Screening	Cycle 1				Cycle 2				Cycle 3	Cycles 4 to X		Treatment Discontinuation	UNS
Day	≤21d prior to C1 (D1)	D1	D3	D8	D15	D1	D3	D8	D15	D1	D1	D8	-	
Visit window		+3d	+2d	±1d	±1d	±3d		±1d	±1d	±3d	±3d	±1d		
Tumor biopsy	X[b]							X[b]						X[h]
Cytokines		X[c]	X	X		X[c]	X	X		X				X[h]
Immunophenotyping (whole blood)		X	X	X	X	X	X	X	X	X	X[e]	X[d]	X	X[h]
PBMCs		X		X	X	X		X	X	X	X[e]	X[d]	X	X[h]
Proteomics (sCD27)		X												
ctDNA		X								X			X	X[h]
DNAseq		X												
Receptor occupancy		X	X	X	X	X				X				
Complement (C3a and Bb)		X[f]		X		X[f]		X		X[g]				

C=cycle; ctDNA=circulating tumor-derived deoxyribonucleic acid; D/d=day(s); DNAseq= deoxyribonucleic acid sequencing; FFPE=formalin-fixed, paraffin embedded; PBMC=peripheral blood mononuclear cell; sCD27=soluble CD27; UNS=unscheduled.

a. All samples will be collected predose unless otherwise specified.
b. In the Dose Escalation phase 1a, all subjects must provide a FFPE tumor tissue sample from a fresh tumor biopsy. A fresh biopsy is defined as being taken after failure/stop of last prior treatment and within 6 months prior to C1D1. Documentation of fresh 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 GEN1053. All subjects should also provide an archival tissue sample (FFPE/slides) if available, preferably from advanced disease stage. An on-treatment biopsy is also required between Cycle 2 Day 8 and Cycle 2 Day 21 (inclusive) of GEN1053 monotherapy. Core needle or excisional biopsies, or resected tissue are required. Fine needle aspirates are not sufficient. The following specimen types are not acceptable biopsy samples: cytological specimens, aspirates, bone, or bone marrow (Section 8.7.2). Details of the preparation and number of slides to be prepared will be described in the laboratory manual. If deemed necessary by the investigator, the enrolled subject may be called in for an unscheduled visit where additional tumor biopsies may be collected.
c. Collected preinfusion on Cycle 1 Day 1 and Cycle 2 Day 1, and at 2 hours and 4 to 6 hours post infusion.
d. Cycle 4 only.
e. Preinfusion sample to be collected at even number cycles (eg, Cycle 4, Cycle 6, Cycle 8, Cycle 10).
f. Preinfusion and 4 to 6 hours post infusion.
g. Preinfusion on Day 1 and on Days 8 and 15.
h. Optional

Table 1-4 Vital Signs – Dose Escalation – GEN1053 Monotherapy

Preinfusion (up to 30 min before infusion)
15 minutes after start of infusion (±5 minutes)
At the end of infusion (±5 minutes)[a]
30 minutes after end of infusion (±5 minutes)
1 hour after end of infusion (±10 minutes)
2 hours after end of infusion (±10 minutes)
4 hours after end of infusion (±10 minutes)[b]

Further assessment details are provided in Section 8.3.3.
a. If infusion lasts for more than 60 minutes, vital signs should be assessed every 15 minutes (±5 minutes) for the remaining duration of the infusion.
b. Vital signs should only be assessed until 4 hours after end of infusion for the first 2 infusions.

1.3.2 Dose Escalation (Combination Therapy)

Schedules of assessments will be provided with selection of the IM combination therapy for each of the placeholder tables in this section upon amending the protocol.

Table 1-5 Schedule of Activities – Dose Escalation – GEN1053+IM Combination Therapy

Table 1-6 PK, ADA, and ECG Sampling – Dose Escalation – GEN1053+IM Combination Therapy

Table 1-7 Biomarker Evaluation Schedule – Dose Escalation – GEN1053+IM Combination Therapy

Table 1-8 Vital Signs – Dose Escalation – GEN1053+IM Combination Therapy

1.3.3 Expansion (Monotherapy)

Table 1-9 Schedule of Activities – Expansion – Subjects With HNSCC – GEN1053 Monotherapy

Cycle/Visit	Protocol Section	Screening	Cycles 1-2				Cycles 3-4			Cycles 5 to X[g]	Treatment Discontinuation	SFU1	SFU2	Survival Follow-up	UNS
Day		≤21 days prior to Visit C1 (D1)	D1	D3	D8	D15	D1	D8	D15	D1	-	30 days after last dose of trial treatment	60 days after last dose of trial treatment	Every 12 weeks after last dose of trial treatment	
Visit Window			+3d[b]	+2d	±1d	±1d	±3d	±1d	±1d	±3d	-	+5d	±7d	±14d	
Informed consent	Appendix 1	X[a]													
Eligibility criteria	5	X													
Demographics	8.1.1	X													
Diagnosis and disease status	8.1.2	X													
Medical history	8.1.3	X													
Height	8.3.2.1	X													
Body weight	8.3.2.2	X	X				X			X	X				
Physical examination	8.3.1	X	X		X[d]	X[d]	X	X[d]	X[d]	X	X	X			X[c]
Vital signs[e]	8.3.3, Table 1-12	X	X		X	X	X	X[d]	X[d]	X	X	X			X[c]
ECG	8.3.4		X[f]				X[f]			X[f]	X	X	X		X[c]
CT/MRI scan	8.2	X	See Section 8.2												
Prebaseline imaging scans and labs	8.2.3, 8.3.6	X													
ECOG PS	8.3.5	X	X				X			X	X	X			X[c]
Adverse events	8.4, 8.4.6	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
Prior and concomitant medications	6.6	X	X	X	X	X	X	X	X	X	X	X	X		X[c]
GEN1053 administration[h]	6		X				X			X					
End of treatment	7										X				
New anticancer treatment	7.1.1										X	X	X	X	
Survival follow-up	7.1.2													X	
LOCAL LABORATORY ASSESSMENTS															

Cycle/Visit	Protocol Section	Screening	Cycles 1-2				Cycles 3-4			Cycles 5 to X[g]	Treatment Discontinuation	SFU1	SFU2	Survival Follow-up	UNS
Day		**≤21 days prior to Visit C1 (D1)**	**D1**	**D3**	**D8**	**D15**	**D1**	**D8**	**D15**	**D1**	-	**30 days after last dose of trial treatment**	**60 days after last dose of trial treatment**	**Every 12 weeks after last dose of trial treatment**	
Visit Window			**+3d[b]**	**+2d**	**±1d**	**±1d**	**±3d**	**±1d**	**±1d**	**±3d**	-	**+5d**	**±7d**	**±14d**	
Hematology	8.3.6, Table 10-1	X[i]	X[j]	X	X	X	X[j]	X	X	X[j]	X	X	X		X[c]
Biochemistry	8.3.6, Table 10-1	X[i]	X[j]	X	X	X	X[j]	X	X	X[j]	X	X	X		X[c]
Coagulation factors	8.3.6, Table 10-1	X[i]	X[j]	X	X	X	X[j]	X	X	X[j]	X	X	X		X[c]
Endocrine	8.3.6, Table 10-1	X[i]	X[j]				X[j]			X[j]	X				X[c]
Urinalysis	8.3.6, Table 10-1	X[i]	X[j]				X[j]			X[j]	X	X	X		X[c]
Pregnancy test	8.3.6, Table 10-1	X[i]	X[j]				X[j]			X[j]	X	X	X		X[c]
Hepatitis B	8.3.6, Table 10-1	X[i]									X				X[c]
CENTRAL LABORATORY ASSESSMENTS															
PK/ADA sampling	8.5	See Table 1-10													
Biomarkers	8.7	See Table 1-11													

ADA= antidrug antibody; C=cycle; CT=computed tomography; D/d=day(s); ECG= electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group performance status; MRI=magnetic resonance imaging; PK= pharmacokinetic(s); SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.

a. Informed consent must be obtained prior to the screening period.
b. Visit window (+3d) applies to Cycle 2 Day 1 only.
c. Optional.
d. A physical examination and vital signs should only be performed as indicated by the subject's symptoms, adverse events, or other findings as determined by the investigator.
e. Temperature, blood pressure, and heart rate should be measured according to Table 1-12 on infusion days. On noninfusion days, vital signs should be obtained any time during the visit.
f. On infusion days, ECG before infusion and at the end of infusion + 2 hours (± 15 minutes). ECG must be obtained at Cycles 1 through 3, Cycle 5, Cycle 7, and every 4 cycles thereafter.
g. In case of PD on GEN1053 monotherapy, subjects will have the option to cross over to combination therapy with GEN1053+IM when the IM has been selected (Table 1-13).
h. Refer to Section 6.7.2.3 for details on post GEN1053 infusion precautions and observation periods.
i. All local laboratory samples at the screening visit must be obtained within 7 days prior to Cycle 1 Day 1 (with the exception of hepatitis B sample, which may be obtained earlier).
j. Local laboratory samples should be obtained on Day 1 of each cycle or no more than 3 days before the visit for Cycle 2 and beyond and reviewed before dosing.

Table 1-10 PK and ADA Sampling – Expansion – Subjects With HNSCC – GEN1053 Monotherapy

Cycle/Visit	Screening	Cycle 1		Cycle 2	Cycle 3	Cycles 4 to X	Treatment Discontinuation	SFU1	SFU2	UNS
Day	≤21 days prior to Visit C1 (D1)	D1	D3	D1	D1	D1	-	30 days after last dose of trial treatment	60 days after last dose of trial treatment	-
Visit Window			+2d	+3d	±3d	±3d		+5d	±7d	
PK Sampling (Section 8.5)										
Preinfusion (on infusion days)		X		X	X	X	X	X	X	X[b]
EOI GEN1053 + 5 min (+ 5 min)		X		X	X	X				
EOI + 2 hr (± 30 min)		X			X					
EOI + 4 hr (± 1 hr)		X								
EOI + 48 hr (+ 2 days)			X							
ADA Sampling (Section 8.8)										
Preinfusion (on infusion days)		X		X	X	X[a]	X	X	X	X[b]

ADA=antidrug antibody; C=cycle; D/d=day(s); ECG=electrocardiogram; EOI=end of infusion; hr=hours; min=minutes; PK=pharmacokinetic(s); SFU1=safety follow-up visit 1; SFU2=safety follow-up visit 2; UNS=unscheduled.
Note: Clock time must be recorded for infusion start and stop, and for each sample collected.
a. ADA sample at even-numbered cycles only.
b. Optional.

Table 1-11 Biomarker Evaluation Schedule – Expansion – Subjects With HNSCC – GEN1053 Monotherapy

Cycle/Visit[a]	Screening	Cycle 1				Cycle 2				Cycle 3	Cycles 4 to X		Treatment Discontinuation	UNS
Day	≤21d prior to C1 (D1)	D1	D3	D8	D15	D1	D3	D8	D15	D1	D1	D8	-	
Visit window		+3d	+2d	±1d	±1d	±3d		±1d	±1d	±3d	±3d	±1d		
Tumor biopsy	X[b]							X[b]						X[h]
Cytokines		X[c]	X	X		X[c]	X	X		X				X[h]
Immunophenotyping (whole blood)		X	X	X	X	X	X	X	X	X	X[e]	X[d]	X	X[h]
PBMCs		X		X	X	X		X	X	X	X[e]	X[d]	X	X[h]
Proteomics (sCD27)		X												
ctDNA		X								X			X	X[h]
DNAseq		X												
RNA blood (GEP)		X		X				X					X	X[h]
Complement (C3a and Bb)		X[f]		X		X[f]		X		X[g]				

C=cycle; ctDNA=circulating tumor-derived deoxyribonucleic acid; D/d=day(s); DNAseq= deoxyribonucleic acid sequencing; FFPE=formalin-fixed, paraffin embedded; GEP=gene expression profile; PBMC=peripheral blood mononuclear cell; RNA=ribonucleic acid; sCD27=soluble CD27; UNS=unscheduled.

a. All samples will be collected predose unless otherwise specified.
b. In the Expansion part, all subjects must provide a FFPE tumor tissue sample from a fresh tumor biopsy. A fresh biopsy is defined as being taken after failure/stop of last prior treatment and within 6 months prior to C1D1. Documentation of fresh 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 GEN1053. All subjects should also provide an archival tissue sample (FFPE/slides) if available, preferably from advanced disease stage. An on-treatment biopsy is also required between Cycle 2 Day 8 and Cycle 2 Day 21 (inclusive) of GEN1053 monotherapy. Core needle or excisional biopsies, or resected tissue are required. Fine needle aspirates are not sufficient. The following specimen types are not acceptable biopsy samples: cytological specimens, aspirates, bone, or bone marrow (Section 8.7.2). Details of the preparation and number of slides to be prepared will be described in the laboratory manual. If deemed necessary by the investigator, the enrolled subject may be called in for an unscheduled visit where additional tumor biopsies may be collected.
c. Collected preinfusion on Cycle 1 Day 1 and Cycle 2 Day 1, and at 2 hours post infusion
d. Cycle 4 only
e. Preinfusion sample to be collected at even number cycles (eg, Cycle 4, Cycle 6, Cycle 8, Cycle 10).
f. Two samples: Preinfusion and 4 to 6 hours post infusion.
g. Preinfusion on Day 1 and on Days 8 and 15.
h. Optional

Table 1-12 Vital Signs – Expansion – Subjects With HNSCC – GEN1053 Monotherapy

Preinfusion (up to 30 minutes before infusion)
At the end of infusion (±10 minutes)[a]
30 minutes after end of infusion (±5 minutes)
1 hour after end of infusion (±10 minutes)
2 hours after end of infusion (±15 minutes)

a. If infusion lasts for more than 60 minutes, vital signs should be assessed every 15 minutes (±5 minutes) for the remaining duration of the infusion.

1.3.4 Expansion (Combination Therapy)

Schedules of assessments will be provided with selection of the IM combination therapy for each of the placeholder tables in this section.

Table 1-13 Schedule of Activities – Expansion – Crossover Subjects With HNSCC – GEN1053+IM Combination Therapy

Table 1-14 Schedule of Activities – Expansion – Subjects With NSCLC – GEN1053+IM Combination Therapy

Table 1-15 PK and ADA Sampling – Expansion – Crossover Subjects With HNSCC – GEN1053+IM Combination Therapy

Table 1-16 PK and ADA Sampling – Expansion – Subjects With NSCLC – GEN1053+IM Combination Therapy

Table 1-17 Biomarker Evaluation Schedule – Expansion – Crossover Subjects With HNSCC – GEN1053+IM Combination Therapy

Table 1-18 Biomarker Evaluation Schedule – Expansion – Subjects With NSCLC – GEN1053+IM Combination Therapy

Table 1-19 Vital Signs – Expansion – Subjects With NSCLC and Crossover Subjects With HNSCC – GEN1053+IM Combination Therapy

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 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 immune checkpoint blockade 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 is rational for improving outcomes to immune checkpoint blockade (CCI ; Nowicki et al., 2018).

GEN1053/BNT313 is jointly developed by Genmab and BioNTech and is an agonistic CD27 antibody designed to (re)activate and increase antitumor immunity through potent induction of costimulatory signaling by FcγR-independent CD27 clustering on the surface of activated T cells.

In nonclinical studies, GEN1053 showed superior capacity to increase proliferation and cytotoxic activity of activated T cells in vitro compared to benchmark CD27 antibodies. Moreover, GEN1053 showed improved capacity to increase the frequency of antigen-specific CD8+ T cells in vivo. Thus, GEN1053 is hypothesized to be more potent than other CD27 antibodies in the clinic. CD27-targeting antibodies in clinical development are often combined with immune CPIs or other immune stimulating agents to enhance antitumor responses. GEN1053 is also expected to be a suitable combination partner for another immunomodulating agent. Provided that the safety profile of GEN1053 monotherapy is acceptable, it is planned to amend this protocol to also explore the safety and efficacy of GEN1053 in combination with another immunomodulating agent. CCI Further details supporting the combination of GEN1053 with an IM are provided in Section 2.2.3.

The aim of this FIH trial for GEN1053 is to investigate the safety, establish the MTD/MAD, and determine the RP2Ds of both GEN1053 monotherapy and GEN1053+IM combination therapy in a sequential manner in a dose escalation setting in patients with solid tumors. 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. Additional doses/schedules and combination compounds may be explored in separate cohorts based on emerging data; randomization between relevant cohorts will be considered.

2.2 Background

2.2.1 Overview of the Indications

2.2.1.1 Head and Neck Squamous Cell Carcinoma

Over 600,000 cases of HNSCC are diagnosed annually worldwide. In 2020, it was estimated that approximately 65,630 new cases of oral cavity, pharyngeal, and laryngeal cancers would be

diagnosed and that 14,500 deaths would occur over the same period in the US (NCCN, 2021b). Tobacco use, alcohol use, and HPV infection increase the risk of developing HNSCC. Patients with locally HPV-positive HNSCC have improved treatment outcomes compared with patients with HPV-negative disease. For patients with recurrent or metastatic HNSCC eligible for immunotherapy/combination therapy, pembrolizumab in combination with platinum (cisplatin or carboplatin) plus 5-FU or pembrolizumab monotherapy (for patients with PD-L1, CPS ≥1) are the recommended 1L regimens. 2L options include doublet cytotoxic chemotherapy regimens, with or without concurrent or sequential cetuximab; however, the mOS is less than 15 months (NCCN, 2021b). Therefore, HNSCC remains an area of high unmet medical need and further opportunity exists to improve outcomes with novel treatment approaches.

2.2.1.1.1 Rationale for HNSCC as the Selected Indication

The MoA of GEN1053 as monotherapy will be explored in a dedicated MoA cohort in the Expansion phase in subjects with recurrent, unresectable, or metastatic HNSCC, allowing easy access to biological material and paired biopsies (at baseline and on-treatment) for biomarker analysis.

A PR (59% shrinkage) has been documented with varlilumab 10 mg/kg + nivolumab 3 mg/kg (CD27 mAb + CPI) in a recurrent/refractory HNSCC subject who had no prior anti-CPI therapy and low PD-L1 (5%) tumor expression in a phase 1/2 study CCI. As pembrolizumab is approved in 1L as monotherapy (PD-L1 CPS>1), or in combination with chemotherapy in PD-L1 allcomers and as single-agent for recurrent/metastatic HNSCC with PD on or after platin-based chemotherapy (allcomers), there is a potential to treat these CPI-resistant patients having limited treatment options with GEN1053 in 2L+ to reactivate their immune response.

Upon PD while on GEN1053, subjects in the HNSSC Expansion cohort will have the option to cross over to GEN1053+IM combination therapy for potential benefit/synergy over monotherapy. Based on nonclinical findings, patients who do not respond to GEN1053 may respond to GEN1053+IM combination as a potential result of optimal agonism or activating diverse pathways that may overall elicit a better antitumor immune response. For instance, GEN1053 mediated increase of IFN-γ CCI. Therefore, sequencing of GEN1053 followed by GEN1053+IM will be explored, as combination therapy with CPI after GEN1053 monotherapy is expected to provide further benefit to patients (see Section 2.2.3).

2.2.1.2 Non–Small-Cell Lung Cancer

Lung cancer is the second most common malignancy with an estimated age-standardized incidence rate of 22.4 per 100,000 and is a leading cause of cancer death for both men and women (Kantar, 2021). Worldwide, approximately 2,206,771 new cases of lung cancer and 1,796,144 deaths were estimated in 2020 (GLOBOCAN, 2020). NSCLC accounts for 85% to 90% of all cases, with a 5-year survival rate of approximately 18% across all stages of the disease, and a rate of only 3.5% for metastatic disease (Jemal et al., 2011; Kantar, 2021; SEER, 2018). In the 1L setting, treatment typically consists of platinum-based chemotherapy in combination with immunotherapy, or a targeted therapy, depending on molecular and biomarker analysis and the histology of the tumor (NCCN, 2021c). More recently, the advent of PD-1 and PD-L1 inhibitors have improved outcomes for patients without driver mutations (approximately 62% of the nonsquamous population and 77% of the squamous population (Kantar, 2021)).

More treatment alternatives are needed for patients whose tumors do not harbor certain oncogenic mutations or do not express the biomarker for CPI options. Novel combinations with complementary approaches to enhance response may further address the unmet need in this population. For patients in the 2L setting, standard of care is typically limited to platinum-based chemotherapy, a CPI monotherapy or docetaxel, with or without ramucirumab, depending on the previous therapy received. For patients in the 3L setting, chemotherapy monotherapy is the standard. Novel therapies are needed to limit toxicity and potentially enhance efficacy in this population (NCCN, 2021c).

2.2.1.2.1 Rationale for NSCLC as Selected Indication

CD27 and CD3D mRNA expression across 30 solid tumor indications available in the cancer genome atlas (TCGA) database was analyzed in silico. CD3D expression (a proxy for T-cell infiltration) was used to rank indications that are infiltrated with T-cells (ie, hot tumors). NSCLC was part of the top three of the listed indications with high CD27 expression. Moreover, more than 60% of the NSCLC patients in this database also showed both high CD27 and CD3D mRNA expression.

Nonclinically, GEN1053 in combination with an IM showed increased T-cell proliferation, cytokine production and cytotoxicity in vitro and expansion of TIL, particularly $CD8^+$ T-cells from NSCLC tumor biopsies ex vivo (GEN1053 IB).

By combining GEN1053 with IM, the aim is to demonstrate an acceptable safety profile and improved clinical efficacy compared to single-agent therapy in subjects with metastatic NSCLC tumors who have progressed on prior treatment with a PD-1/-L1 inhibitor.

2.2.2 Rationale for the Development of GEN1053

CD27 is an important costimulatory receptor on T cells. The activation of costimulatory receptors is required to unlock T-cell effector functions upon cognate antigen recognition on the surface of APCs in the context of MHC molecules. In an active immune response, CD27 clustering is induced upon binding to CD70, the only known CD27 ligand, resulting in triggering of intracellular signaling pathways that enhance proliferation, differentiation, cytokine production, and survival of activated T cells (van de Ven and Borst, 2015).

Several CD27 agonist antibodies are being or have been tested in the clinic (CCI ; Burris et al., 2017; He et al., 2013). These antibodies generally show an acceptable safety profile but limited antitumor activity as monotherapy in solid cancers. CD27 antibodies tested in the clinic thus far are, at least partially, dependent on interactions with FcγR-positive cells to induce CD27 clustering and agonism (Starzer and Berghoff, 2020). The frequency of FcγR-positive cells in the TME may be variable and insufficient to drive optimal CD27 agonism. Moreover, CD27 antibodies with an active Fc domain may induce FcγR-mediated effector functions such as ADCC or ADCP leading to elimination of $CD27^+$ effector T cells.

GEN1053 is an agonistic CD27 antibody designed to (re)activate and increase antitumor immunity through potent induction of costimulatory signaling by FcγR-independent CD27 clustering on the surface of activated T cells. GEN1053-induced CD27 agonism is facilitated by a hexamerization-enhancing mutation in the human IgG1 Fc domain of GEN1053 (Genmab proprietary HexaBody® platform) that drives clustering of membrane-bound antibodies.

GEN1053 has a functionally inactive Fc domain, thereby avoiding potential kill of $CD27^+$ effector cells through Fc-mediated effector functions such as ADCC, ADCP, or CDC.

2.2.2.1 Summary of Nonclinical Studies - Monotherapy

A nonclinical data package, consisting of nonclinical pharmacology and toxicology studies in vitro, in vivo, and ex vivo, is available for GEN1053:

- GEN1053 binds human CD27 with an affinity in the nanomolar range and showed dose-dependent binding to $CD27^+$ human $CD4^+$ and $CD8^+$ T cells.
- In vitro, GEN1053 increased proliferation of human healthy donor T cells that had been activated through TCR crosslinking with EC_{50} values in the subnanomolar range. GEN1053 showed increased potency compared to benchmark IgG1 CD27 antibodies. CD27 agonist activity of GEN1053 was independent of the presence of FcγR-mediated crosslinking in contrast to benchmark antibodies.
- GEN1053 increased T-cell proliferation, activation, and cytokine production in the presence of an enhanced PD-1/PD-L1 signaling axis.
- GEN1053 did not induce T-cell proliferation in the absence of TCR crosslinking.
- Ex vivo, GEN1053 increased the number of tumor-infiltrating lymphocytes in primary NSCLC tumor cultures. Moreover, vaccination studies in hCD27 transgenic mice demonstrated that GEN1053 was able to enhance the T-cell–mediated immune response in vivo.
- GEN1053 increased expression of T-cell activation markers (4-1BB, CD107a, CD69, CD25) and the production of IFN-γ, IL-1β, IL-6, IL-13, GM-CSF, and TNF-α in activated T cells in vitro.
- GEN1053 increased expression of the cytotoxicity-associated molecules GzmB and CD107a on T cells after exposure to tumor cells expressing their cognate antigen, with EC_{50} values in the low nanomolar range. Moreover, GEN1053 increased antigen-specific tumor-cell kill in vitro.

The nonclinical pharmacology results support the premise that GEN1053 has the potential to increase antitumor effects in solid tumor indications that benefit from (re)activation of antitumor T-cell immunity.

<u>Nonclinical Safety Studies:</u>

Two repeat-dose IV toxicology studies (DRF and pivotal GLP) were conducted in cynomolgus monkeys with GEN1053 using dose levels of 0 (vehicle), 0.2 (DRF only), 1, 5, and 30 mg/kg (IV, 30 min infusion; DRF: 4 doses QW; GLP: 3 doses Q3W).

- The main adverse effect in the monkeys was severe thrombocytopenia, which became apparent from 10 to 12 days after the first dose and was followed by severe anemia, prolonged coagulation time, widespread bleeding with hemorrhagic diathesis, and led to

premature sacrifice of several monkeys in the studies. Some plasma biomarkers, including transaminase levels, indicated associated liver function changes. Because of these adverse effects, the monkeys in the GLP study at 5 and 30 mg/kg could be dosed only once.

- Due to adverse findings at all dose levels, the NOAEL or HNSTD for GEN1053-induced adverse effects could not be determined in the pivotal GLP toxicology study.

In a series of in vitro studies with human and/or cynomolgus monkey blood cells or tissues, it was shown that GEN1053 only binds to tissues known to express CD27 (T cells, NK cells, induced B cells); in particular, no binding of GEN1053 to red blood cells, platelets, megakaryocytes, or megakaryoblasts was detected. When incubated with human whole blood, GEN1053 did not induce cytokine release, hematological changes, hemolysis, or clumping/precipitation in the plasma.

The mechanism behind the adverse hematological effects observed in the cynomolgus monkey toxicology studies (thrombocytopenia, coagulation changes, anemia, bleeding, etc) is uncertain. Possible mechanisms could be platelet aggregation caused by GEN1053-induced ADAs that were rapidly cleared due to immune complex formation and thus not detected, or CD27-related exaggerated pharmacology affecting the lymphoid cells and bone marrow function at the high dose levels employed in the monkey studies.

A more detailed description of the nonclinical safety findings for GEN1053 is provided in the IB.

Based on the findings in nonclinical safety studies with GEN1053, a very cautious approach for the FIH clinical trial with GEN1053 has been implemented to ensure proper observation, handling and mitigation of potential toxicities detected in the nonclinical safety program:

- CCI [redacted]
- A cautious dose-escalation procedure for the initial part of the FIH clinical trial
- Close monitoring of hematology and coagulation systems as well as of hepatic function and PK characterization in the subjects (including RBC/Hb, PLT, APTT/PT, ALT, CRP, complement factors (C3a and Bb), PK, and ADAs)

Further details on mitigation of potential toxicities are provided in Section 2.3.

2.2.3 Rationale for the Evaluation of GEN1053 in Combination With an IM

To improve the antitumor efficacy of CCI [redacted], most of the current CCI [redacted] in clinical development are evaluating combination strategies with other anticancer therapies, including T-cell costimulatory receptor agonists CCI [redacted]. Activation of T-cell costimulatory receptors (ie, CD27 CCI [redacted]) can amplify the effect of CCI [redacted], as shown nonclinically and in CCI [redacted]. Patients who have received CCI [redacted] therapy may develop CCI [redacted] Costimulation through CCI [redacted] may support re-establishing antitumor immunity in this patient population CCI [redacted]

CCI . CD27 costimulation in combination with CCI showed clinical activity in tumor types resistant to CCI . In addition, CD27 in combination with CCI leading to tumor growth inhibition that was not seen with either CD27 CCI monotherapy. CCI

T-cell costimulation via CCI agonistic antibodies alone can enhance antitumor memory T-cell survival resulting in longer lasting protective immunity against the tumor CCI . Furthermore, CCI antibodies can complement T-cell costimulation CCI , which may improve antitumor responses in patients with insufficient baseline T-cell activation CCI . Therefore, it is hypothesized that coactivation of CD27 with CCI may further improve antitumor responses and thereby the clinical benefit for patients.

CCI

- CCI
- CCI
- CCI

Additional details including results from nonclinical combination studies, are provided in the GEN1053 IB and any updates thereof.

The optimal combination partner(s) will be selected based on the monotherapy safety profile of GEN1053 and emerging data from the compounds CCI . The protocol will be amended before initiating the combination therapy Dose Escalation phase 1b.

2.2.3.1 Summary of Nonclinical Studies – Combination Therapy

A nonclinical data package, consisting of nonclinical pharmacology studies in vitro and ex vivo is available for the combination of GEN1053 with CCI .

Nonclinically, GEN1053 in combination with CCI showed increased capacity to increase proliferation and cytokine production in activated T cells in vitro. In addition, combination of GEN1053 with CCI enhanced cytotoxicity in vitro and

expansion of TIL, particularly $CD8^+$ T cells, from NSCLC tumor tissue ex vivo (GEN1053 IB, Section 3).

2.2.4 Summary of Clinical Trials to Date and Experience With CD27-Targeting Agents

2.2.4.1 GEN1053 Clinical Trials

This is the FIH trial of GEN1053. There are no other ongoing or completed clinical trials.

2.2.4.2 Experience With CD27-Targeting Drugs

To date, other CD27-targeting mAbs in clinical development, varlilumab (CDX-1127, Celldex Therapeutics) and MK-5890 (Merck), have shown early antitumor activity in subjects with advanced solid tumors in monotherapy CCI [redacted]. Importantly, they have demonstrated an acceptable safety profile in FIH trials as monotherapy CCI [redacted].

In clinical safety data from other CD27-agonist compounds studied in monotherapy for solid tumors, the most frequently observed AEs included fatigue, rash, nausea, diarrhea, pruritus, and IRRs. Most of these events were mild or moderate in severity. Refer to the GEN1053 IB for available safety information from other CD27-targeting agents.

2.3 Benefit-Risk Assessment

2.3.1 Potential Benefit

2.3.1.1 Potential Benefit of GEN1053

Based on nonclinical data and published clinical data regarding other agents that target human CD27 mAbs in various tumor types, clinical antitumor activity can be expected for GEN1053. Therefore, cancer patients with limited treatment options, and for whom the investigator agrees that clinical trial participation is appropriate, may benefit from treatment with GEN1053.

2.3.1.2 Potential Benefit of GEN1053 in Combination With IM

Based on their respective MoAs, it is hypothesized that the combination of GEN1053 with an IM will enhance the antitumor activity as compared with GEN1053 monotherapy (Section 2.2.3.1).

Further details will be provided in a substantial amendment before initiating phase 1b of the trial.

2.3.2 Potential Risks

2.3.2.1 Potential Risks of GEN1053

The nonclinical studies performed with GEN1053 demonstrated thrombocytopenia, bleeding, anemia, and increased plasma levels of ALT, AST, and LDH with delayed onset in monkeys. The exact MoA has not yet been determined. However, there was no cytokine release, hemocompatibility issues, or direct binding of GEN1053 to human or cynomolgus monkey platelets and erythrocytes detected. Possible mechanisms could be platelet aggregation caused by

GEN1053-induced ADAs that were rapidly cleared due to immune complex formation and thus not detected, or CD27-related exaggerated pharmacology affecting the lymphoid cells and bone marrow function at the high dose levels employed in the monkey studies. Overall, based on the observed toxicities in monkeys, additional safety measures will be taken when exploring GEN1053 in the first clinical trial.

A mitigation plan for handling AEs, including elevated liver parameters, CRS, IRRs, and thrombocytopenia, related to the trial treatment has been prepared for this trial to closely monitor for and ensure dose delay, dose reduction, or withdrawal of subjects based on AEs that may occur during trial treatment (Section 6.7.2).

Risk mitigation strategies are provided in Section 6.7.2 and summarized in Section 2.3.3.

Targeting CD27 has not in itself led to unacceptable toxicities or safety concerns with other compounds in clinical development (see Section 2.2.4.2).

Potential subjects will be fully informed of the risks and requirements of the trial, and during the trial, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the trial is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the trial and provide their consent voluntarily will be enrolled.

GCT1053-01 phase 1a data showed an increased frequency of severe cytopenias and severe transaminase increases in subjects treated with GEN1053 with prior anti-PD-1/PD-L1 exposure within the last 6 months. Due to this potential risk subjects treated with anti-PD-1/PD-L1 within the last 6 months are excluded from participation in the trial.

Further details are provided in the IB and its updates thereof. Currently, there are no anticipated events for GEN1053 described in the reference safety information. Additional safety information collected between IB updates will be communicated in the form of investigator notifications.

2.3.2.2 Potential Risks of Immunomodulators

For combination therapy, the potential risk of overlapping toxicities depends on the MoA of the therapies to be combined with GEN1053. When the IM has been selected, such risk consideration will be made, and a substantial amendment of this protocol will be submitted and subject to approvals by health authorities and IRBs/ethics committee prior to initiating the GEN1053+IM combination Dose Escalation phase 1b of the trial.

2.3.3 Conclusion

Based on the interpretation of the nonclinical data available to date, published data from other CD27-targeting agents, and the potential IM candidates, the conduct of this trial investigating GEN1053 monotherapy and GEN1053+IM sequentially is regarded as justifiable.

A cautious approach will be applied for dose escalation from CCI [redacted] in this FIH trial with strict DLT criteria, adequate AE management, and safety stopping rules in place (see Sections 6.7.1 and 6.7.2).

The population eligible for the current 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 GEN1053 or GEN1053+IM may be beneficial. The trial population is defined to include only subjects with a platelet count $\geq 150 \times 10^9$/L at baseline. Subjects with known platelet function defects or a known history or high risk of bleeding events requiring transfusions or hospitalizations will also be excluded from the trial.

Events to be closely monitored for GEN1053 include thrombocytopenia, bleeding episodes, elevated liver parameters, irAEs, and IRRs. The DEC (during the escalation phases 1a and 1b) and the SC (throughout the trial) will closely monitor subject safety as described in Appendix 1. In addition, an independent DMC will further supervise that the safety of the subjects in this trial is properly safeguarded, acting as an external advisory body (Appendix 1).

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 GEN1053 and the selected IM(s) (Section 6, Table 6-2, Table 6-3 and Table 6-4). 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 professional(s) who will provide care and closely evaluate each subject's response to GEN1053 and GEN1053+IM both in terms of safety profile and efficacy.

Collectively, the benefit-risk ratio is considered favorable for GEN1053.

The sponsor is committing to sharing relevant monotherapy safety data from the monotherapy Dose Escalation phase 1a part with the health authorities and to submitting a substantial amendment before initiating the phase 1b combination Dose Escalation part of the trial.

For further details on GEN1053, refer to the IB.

3 OBJECTIVES AND ENDPOINTS

Objectives and endpoints by study part are summarized in Table 3-1.

Table 3-1 Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
• Determine MTD/MAD/RP2Ds of GEN1053 as monotherapy and in combination with IM • Establish initial safety profile of GEN1053 as monotherapy and in combination with IM	• DLT(s) (Dose Escalation parts only) • AEs and safety laboratory parameters
Secondary	
• Establish PK profile of GEN1053 as monotherapy and in combination with IM	• PK parameters for GEN1053: CL, V, C_{max}, t_{max}, C_{trough}, $t_{1/2}$, AUC_{last} and AUC_{tau}
• Evaluate immunogenicity of GEN1053 as monotherapy and in combination with IM	• Antidrug antibody response to GEN1053 and in combination with IM
• Evaluate antitumor activity of GEN1053 as monotherapy and in combination with IM	Antitumor activity according to RECIST 1.1: • ORR • DCR • DoR
Exploratory	
• To assess pharmacodynamics, potential response and safety biomarkers for GEN1053 as monotherapy and in combination with IM	• Immune system activation (eg, immune subset shift, modulation of activation markers on lymphocytes, changes in TCR clonality, and tumor immune cell infiltration)
• To assess antitumor activity based on iRECIST of GEN1053 as monotherapy and in combination with IM	• Antitumor activity according to iRECIST • iORR • iDCR • iDoR • iPFS
• Evaluate efficacy of GEN1053 as monotherapy and in combination with IM	• PFS • OS
• To assess tumor growth with GEN1053 as monotherapy and in combination with IM	• Change in tumor size

Hypotheses:

The Dose Escalation parts of the trial aim to describe the relationship between dose and toxicities without testing hypotheses. The Expansion part will generate hypotheses regarding efficacy, ORR, and regarding PFS, DCR, and DoR.

Details on statistical considerations are provided in Section 9.

4 TRIAL DESIGN

4.1 Description of Trial Design

This is a FIH phase 1/2a open-label, multicenter, multinational trial in subjects with non-CNS metastatic or advanced solid tumors for whom there is no available standard therapy likely to confer clinical benefit, evaluating the safety, tolerability, preliminary antitumor activity, PK, pharmacodynamics, and immunogenicity of GEN1053 as monotherapy as well as in combination with IM.

The trial will be conducted with a Dose Escalation part (phase 1a and 1b) and an Expansion part (phase 2a) as follows:

- Phase 1a – Monotherapy Dose Escalation
- Phase 1b – Combination therapy Dose Escalation
- Phase 2a – Expansion

The Dose Escalation part will explore the safety of escalating doses of GEN1053 as monotherapy (phase 1a) as well as escalating doses of GEN1053 when combined with a fixed dose of an IM (phase 1b) in a sequential approach in a population of subjects with various solid tumors.

The sponsor will share relevant monotherapy safety data from phase 1a with the health authorities and submit a substantial amendment before initiating the combination Dose Escalation phase 1b.

The Expansion part is planned to provide additional safety and initial antitumor activity information of the RP2Ds for GEN1053 monotherapy and GEN1053+IM combination therapy, respectively, in selected tumor indications. In the first Expansion cohort (HNSCC), more detailed data related to the MoA of GEN1053 monotherapy will be generated. Upon PD while on GEN1053, and provided that the RP2D for the combination has been determined in phase 1b, subjects will have the option to cross over to GEN1053+IM to explore the effect of sequencing the trial treatments. In the second Expansion cohort, GEN1053+IM will be evaluated in subjects with NSCLC.

Each part will consist of a screening period (up to 21 days prior to C1D1), a treatment period (C1D1 until discontinuation of trial treatment), and 2 safety follow-up visits 30 days and 60 days after each subject receives the last dose of trial treatment, preceding the survival follow-up. Subjects will be treated in cohorts, defined as a group of subjects allocated to the same treatment.

Both GEN1053 and IM will per default be administered as an IV infusion in 3-week (ie, 21-day) cycles (Q3W) (refer to Section 6, Trial Treatment) until PD, unacceptable AE, or withdrawal of consent (refer to Section 7.1).

The protocol may be amended to explore additional doses/schedules and combination compounds both during Dose Escalation and/or in separate Expansion cohorts based on emerging data. Randomization between relevant doses/schedules will be considered in the

Expansion part. Such an amended protocol will be submitted as a substantial amendment prior to initiation.

The safety, tolerability, immunogenicity, PK, pharmacodynamics, and biomarkers will be assessed together with the clinical activity of GEN1053 or GEN1053+IM. Assessments, biomarkers, PK, and ADAs will be evaluated as detailed in the Schedule of Activities, Section 1.3.

A trial-independent DMC, an SC, and a DEC will be commissioned for this trial. Refer to the Committees Structure section of Appendix 1 for details.

During the Dose Escalation part, DLTs will be assessed by the DEC in the first treatment cycle of each DL. In case a DLT has been observed at the current dose level, the DEC will assess whether escalation by a half or a full DL is appropriate, depending on the nature of the observed DLT, and supported by the BLRM approach, which is used to make dose recommendations and estimate the MTD during the Dose Escalation part of the trial. The DEC will also assess all available data with focus on safety events that meet DLT criteria but occur after the DLT period in any subject according to the DEC Charter and make recommendations for the next DL and/or propose the RP2D/MTD/MAD to the DMC and the SC. The DMC will assess the totality of information of the trial to propose whether the trial can proceed to the subsequent design phase according to the DMC charter. The SC will make the final decision regarding dose escalation (or de-escalation) and/or the continuation of the trial to its next design phase.

During the Expansion phase of the trial, the SC will make decisions regarding the progression of the trial based on benefit-risk considerations. The SC can also stop further enrollment if treatment-emergent toxicity is determined to result in an unfavorable benefit-risk assessment for subjects. Enrollment may be temporarily stopped, if needed, for the SC to evaluate emerging data. In case of emerging safety issues with potential impact on the trial conduct, the SC will inform and consult the DMC on an ad hoc basis.

The decision process will be guided by the principles outlined in Section 4.2.1 and 4.2.2.

A diagram of the trial design is provided in Section 1.2.

Patient input into trial design was not obtained for this trial.

4.2 Trial Design Rationale

4.2.1 Dose Escalation (GEN1053 Monotherapy)

In the Monotherapy Dose Escalation phase 1a, GEN1053 will be evaluated in non-CNS 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.

The Monotherapy Dose Escalation will potentially (dependent on data collected during the trial) evaluate CCI [redacted]. GEN1053 will be dosed Q3W.

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 SC which are further investigated by backfilling.

Identification of MTD/MAD (Monotherapy):

To address the trial objectives in this FIH trial, the Monotherapy Dose Escalation phase 1a will be initiated in single-subject cohorts for the first 2 DLs followed by 3-subject cohorts for subsequent DLs. However, a 1-subject cohort will be converted to a 3-subject cohort if any of the following events are observed:

- Any grade ≥2 AE within the first 21 days of Cycle 1, unless clearly related to underlying disease or extraneous causes.
- A DLT (see Section 6.7.1) within the first 21 days of Cycle 1.

If cohort conversion occurs at the first DL, the subsequent DLs will be explored in 3-subject cohorts with the option to expand as described below.

To aid in determining the DL for the next cohort, the relationship between the probability of DLT and DL will be described by a 2-parameter BLRM with overdose control (EWOC) (Babb et al., 1998; Neuenschwander et al., 2008). After each cohort, the model parameters will be updated based on the available DLT information and a DL for the next cohort suggested based on the posterior distributions of probabilities of DLTs at each DL. Compared to the standard 3+3 and accelerated titration designs, the BLRM provides both more flexibility and better accuracy of the estimated MTD while ensuring subject safety.

All escalations are constrained (ie, a new DL can only be 1 step higher than the previous DL [intermediate DLs will count as half a step]). De-escalations can skip DLs. The dose escalation is limited to only main DLs until the first DLT is observed; thereafter the intermediate DLs become available. Backfilling of intermediate DLs may also be considered.

The following provides a description for subject accrual and provisions for dose escalation/de-escalation decision guidance.

1. After completion of Cycle 1 of each cohort, based on the cumulative safety data and the BLRM, the SC will endorse the DL for the next cohort of subjects.
2. The initial 2 DLs will be single-subject cohorts. In case of a treatment-related Grade ≥2 AE during the first cycle or a DLT (Section 6.7.1), the cohort(s) will be expanded to 3 subjects and the BLRM method will be applied after first DLT.
3. A subject will be considered as evaluable for dose determination if they fulfil the criteria of the DDS (refer to Section 9.3.4).
4. Once the first DL has been cleared, the BLRM method will be used to support recommendations for the DL for the next cohort, with the following 3 exceptions:
    - If no DLTs have been observed, escalation may be considered.
    - For cohorts requiring ≥3 evaluable subjects, if only 2 evaluable subjects are available for assessment (all others drop out) and neither subject has experienced a DLT, 2 subjects will

be considered sufficient for decision making.

- If 2 subjects in a cohort experience DLTs, the BLRM model will be updated and reevaluated before the enrollment of any additional subject.
- If a decision has been made to escalate to a higher DL, but 1 or more additional subject(s) treated at preceding DLs (see provision 6) experience(s) a DLT in Cycle 1, then the BLRM will be updated before any additional subject is enrolled to the current (higher) DL.

5. Following the principle of EWOC, the BLRM model only allows escalation to DLs that are likely to be safe.
6. For further understanding of the safety, tolerability, and PK of GEN1053, additional cohorts of up to 9 subjects may be enrolled at preceding DLs, or at intermediate DLs before or while proceeding with further dose escalation or even thereafter (backfill subjects). Backfill subjects within a DL can receive their first treatment simultaneously.
7. A cohort may be expanded to enroll additional subjects. This is in order to ensure availability of sufficient data due to the potential for subjects to discontinue therapy during Cycle 1 without DLT (eg, because of early PD) and allow flexibility.
8. After repeating the above steps, the MTD is declared when at least 9 subjects have been evaluated at a DL and the BLRM recommends allocating an additional cohort to the same DL. This DL is the MTD identified by the BLRM. MTD may be declared based on at least 6 subjects if the recommendation is to escalate and the next DL is not available.
9. The dose escalation stops when either the MTD has been declared or no doses are considered safe.

More details on the BLRM can be found in Appendix 8.

The SC (after consultation with the DEC and DMC) will determine the MTD and the RP2D based on the BLRM estimate and the totality of data. The MTD and RP2D may be the same as the algorithm recommends for the next cohort or it may be a lower dose.

If there is evidence that a DL lower than the MTD has adequate efficacy (whether determined by scan data, by pharmacodynamic endpoints, or predicted efficacious dose), the DMC may recommend, and the SC may decide, that an RP2D has been determined and may decide to stop the dose escalation.

The overall decision process for the next DL and/or to propose the RP2D/MTD/MAD based on the above guidance is summarized in Section 4.1.

4.2.2 Dose Escalation (GEN1053+IM)

Identification of first GEN1053 dose to be combined with IM: After the MTD/MAD of GEN1053 as monotherapy has been determined, the first GEN1053 DL to be combined with an IM (at a fixed dose) is targeted to be the MTD/MAD minus at least 2 DLs (MTD-2). The selection of the starting DL for GEN1053 for combination with IM will follow the decision process summarized in Section 4.1.

Upon selection of the GEN1053 start dose and IM for combination therapy, a substantial amendment will be issued. This amendment will be subject to approvals by health authorities and IRBs/ethics committees, before initiating phase 1b and the Expansion cohort 2 of this trial.

Dose Escalation Principles for GEN1053+IM

In Combination therapy Dose Escalation (GEN1053+IM) phase 1b, escalating doses of GEN1053 (starting from MTD-2) will be evaluated in subjects with non-CNS metastatic or advanced malignant solid tumors in combination with a fixed dose of an IM using a mBOIN design (Liu and Yuan, 2015). DLTs will be assessed at each DL in the first treatment cycle, ie, a DLT evaluation period of 21 days from C1D1.

The minimum number of subjects treated at each DL is 3. Apart from that, the precautions for subject enrollment within a DL in phase 1a of the trial (Section 4.2.1) also apply for phase 1b of the trial.

A limited number of subjects will be enrolled into phase 1b of the trial. This causes operational challenges on applying a BLRM design, which also tends to be conservative in its choice of MTD. Therefore, escalation and de-escalation in the combination Dose Escalation part will be guided by a mBOIN design. Although similar to the 3+3 design, it adds the ability to 1) investigate a DL multiple times that would have been closed in a 3+3 design; 2) repeatedly escalate and de-escalate; and 3) treat more than 6 subjects at a DL. The mBOIN selects the true MTD at a higher rate and treats a higher percentage of the subjects at the MTD.

The DLT rate for a given DL is estimated as total number of DLTs/total number of subjects treated and qualifying for DDS (at that DL). Based on the accrued data (at each DL), the mBOIN decision guidance rules are supplied in Table 4-1. For further details on the mBOIN methodology, please see Appendix 8.

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	0	0	≤1	≤1	≤1	≤1	≤2
	Remain	1	1	-	2	2	2	3
	De-escalate	2	2	2	3	3	3	4
	Terminate a DL	3	≥3	≥3	≥4	≥4	≥4	≥5

DL=dose level; DLT=dose-limiting toxicity.

If de-escalation is mandated, GEN1053 will be decreased to the preceding lower main DL while the IM DL per default will be kept fixed during the combination escalation part of the trial. A dose modification of the IM may be proposed by the DEC, the SC, or the DMC in case of emerging safety concerns for the combination treatment. The SC must endorse any such proposal before implementation. A dose modification of IM will be considered a new escalation combination cohort with a similar number of subjects as in other Combination therapy Dose Escalation cohorts.

The SC (after consultation with the DEC and DMC) will determine the MTD and the RP2D based on the mBOIN estimate and the totality of data. The MTD and RP2D may be the same as the algorithm recommends for the next cohort or it may be a lower dose.

If there is evidence that a DL lower than the MTD has adequate efficacy (whether determined by scan data, pharmacodynamic endpoints, or predicted efficacious dose), the DMC may recommend, and SC may decide, that the RP2D has been determined and may stop the combination therapy dose escalation.

The overall decision process for the next DL and/or to propose the RP2D/MTD/MAD is summarized in Section 4.1 and will also be based on the above guidance and the principles in Sections 4.2.2.2 to 4.2.2.6.

4.2.2.1 Modifications to BOIN

The escalation stops if there are 9 subjects already dosed on next proposed DL.

4.2.2.2 Dose Level Termination

A potential drawback of the basic BOIN design is that, theoretically, a very toxic DL could be investigated in multiple cohorts if a neighboring DL is not toxic. To avoid this problem, a DL termination criterion will be implemented: A certain DL can no longer be investigated if an additional DLT-free cohort would lead to de-escalation. For example, if there are no DLTs at the current DL, but 3 out of 4 subjects had DLTs at the next higher DL, any outcome would lead to de-escalation (regardless of 0, 1, 2, or 3 DLTs, there would be least 3 DLTs for 7 subjects). All DLs with a higher dose than that of the terminated DL should also be terminated.

4.2.2.3 Cohort Size

In the Combination therapy Dose Escalation phase 1b, the mBOIN may be executed if 1 subject is non-DLT evaluable and the remaining 2 subjects are DLT-evaluable, provided that neither of the 2 subjects experience any DLT during the 21-day DLT period. If a DL has a total of 2 subjects who are DLT-evaluable and no DLTs are observed, the mBOIN rule is to escalate.

Additionally, over-recruitment by 1 subject will be allowed, so that each 3-subject cohort may consist of 2 to 4 subjects who are evaluable for DLTs.

In the event a cohort has less than 3 DLT evaluable subjects, the next cohort at the same DL may be expanded to bring the number of subjects at the DL up to a multiple of 3.

4.2.2.4 Stopping Rules

- If the DEC suggests revisiting a DL where 9 subjects have been dosed, the SC may decide to stop further dose escalation.

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

The MTD may be declared based on 6 subjects if the recommendation is to escalate and the next level is not available.

4.2.2.5 Backfill Cohorts

Backfill subjects are those that are added after a DL has been declared as safe, and escalation has proceeded to next higher DL. More than one backfill subject within a DL can therefore receive treatment simultaneously. Additional subjects may be enrolled to backfill DLs that have been cleared for safety 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. Any DLTs observed in such subjects will not directly contribute to the mBOIN design evaluation.

If the mBOIN algorithm later stipulates de-escalation to an over-recruited DL, all subjects on that dose will be included in the mBOIN algorithm.

4.2.2.6 Other Dose Escalation/De-escalation Procedures

The following provides a description of the procedures not directly associated with the mBOIN as such, but that will impact subject accrual and provisions for dose escalation/de-escalation decisions.

1. 1. After completion of Cycle 1 of each DL, based on the safety data and the mBOIN, the SC will endorse the DL for the next cohort of subjects after consideration of the recommendations of the DEC. Escalation to the next DL will not occur until all subjects needed for a specific cohort have passed the Cycle 1/DLT evaluation period.

2. 2. A subject will be considered as evaluable for dose determination if they fulfil the criteria of the DDS (refer to Section 9.3.4).

4.2.3 Expansion

The aim of the Expansion part is to provide further data on the safety, tolerability, MoA, PK, and antitumor activity of the selected RP2Ds and schedules in subjects with recurrent, unresectable, or metastatic HNSCC (GEN1053) and in subjects with metastatic NSCLC (GEN1053+IM), respectively.

In Expansion cohort 1, subjects with recurrent, unresectable, or metastatic HNSCC who have been previously treated with a PD-1/PD-L1 inhibitor and platinum will be treated with the GEN1053 RP2D Q3W until one of the predefined criteria for treatment discontinuation are met. In case of PD (Section 7.1) on GEN1053 monotherapy, subjects in the HNSCC Expansion cohort will have the option to cross over to combination therapy with GEN1053+IM for the potential benefits as summarized in Section 2.2.3, once the GEN1053 RP2D for the combination has been determined.

In Expansion cohort 2, subjects with metastatic NSCLC that have been previously treated with a PD-1/PD-L1 inhibitor will be treated with the RP2D for GEN1053 in combination with IM (both Q3W) until one of the predefined criteria for treatment discontinuation are met.

The Expansion part will enroll approximately 40 subjects within each Expansion cohort.

Additional doses/schedules and combination compounds may be explored in separate cohorts in the Expansion part as data emerges. Randomization between relevant cohorts will be considered. If alternative doses/schedules or other compounds are to be tested in combination with GEN1053, the DMC will be consulted for their recommendation, while the SC will make the final verdict on any such decision that will require an amendment of the protocol.

4.3 Dose and Schedule Rationale

4.3.1 IMP Dose and Schedule Rationale

A starting dose of CCI was selected for this FIH clinical trial of GEN1053. This dose was defined using a CCI

Based on published data of clinical experience, CD27 agonist antibodies are observed to be well tolerated in FIH studies (see Section 2.3.3). CD27 overexpression is observed primarily in activated T cells via the TCR/CD3 pathway. CCI

The FIH starting dose was defined as the dose associated with a CCI

CCI is proposed for use in the GEN1053 FIH trial. CCI

CCI

For further details, see the GEN1053 IB.

4.3.2 AMP Dose and Schedule Rationale

Further details on any AMPs will be provided in a substantial amendment before initiating phase 1b or phase 2a of the trial.

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 one 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 for an Individual Subject

The estimated trial duration for an individual subject is up to approximately 20 months, consisting of a 21-day screening period, an estimated 6-month treatment period (the duration of treatment may vary for each subject), a 60-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), or, for the monotherapy dose escalation part, when the last subject discontinuing treatment has completed the last safety follow-up visit.

4.4.3 End of Trial Definition and Estimated Trial Duration

The end of trial is defined as the date of the last data collection for the last subject in the trial globally. The estimated trial duration is approximately 20 months after the last enrolled subject's first treatment in the trial.

Availability of trial treatment after the end of the trial is covered in Section 6.9.

Individual subject withdrawal criteria are provided in Section 7.2.

5 TRIAL POPULATION

The inclusion and exclusion criteria for enrolling subjects in this trial are described below. For questions regarding these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the trial. Waivers are not allowed.

Note: Investigators, in coordination with the sponsor's medical officer, or delegate, should 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, such that the subject no longer meets all eligibility criteria, then the subject should be excluded from participation in the trial.

5.1 Inclusion Criteria

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

For both the Dose Escalation and Expansion parts

1. Subject (or their legally acceptable representative [not applicable in EU/EEA]) 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 prior to initiating any other trial related assessments or procedures. 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).

Subject must:

2. Be ≥18 years of age.
3. Have measurable disease according to RECIST 1.1.
4. Provide all prebaseline scans since failure of last prior therapy (eg, documented radiographic PD), if available.
5. Have Eastern Cooperative Oncology Group performance status ≤1.
6. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
7. Have organ and bone marrow function as follows:
    a. Bone marrow/hematological function:
        i. ANC ≥1.5×10^9/L
        ii. Hemoglobin ≥9.0 g/dL
        iii. Platelet count ≥150×10^9/L
    b. Liver function:
        i. Total bilirubin ≤ ULN
        ii. ALT ≤1.5×ULN
        iii. AST ≤1.5×ULN
        iv. Albumin ≥30 g/L

c. Coagulation status:

i. PT/INR ≤1.5

ii. aPTT ≤1.5×ULN
Note: Subjects receiving anticoagulant therapies should have PT and aPTT within the therapeutic range of intended use of anticoagulants.

d. Renal function:

GFR ≥45 mL/min/1.73 m², according to the abbreviated MDRD equation:

GFR = 186 × (SCr - 1.154) × (age - 0.203) × (0.742 if female),

where SCr is expressed in mg/dL and the result is multiplied by 1.212 if the subject is Black.

8. A female subject with reproductive potential (postmenopausal or permanently sterilized is considered as not having reproductive potential) must agree to use adequate contraception during the trial and for 6 months after the last administration of GEN1053. Adequate contraception is defined as highly effective methods of contraception (refer to Appendix 4 for more information). In countries where 2 forms of highly effective methods of contraception are required, this will be an inclusion criterion.
9. A female subject with reproductive potential must have a negative serum beta-human chorionic gonadotropin test at screening.
10. A female must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial and for 6 months after the last dose of trial treatment.
11. A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control, eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, during and for 6 months after the last GEN1053 treatment administration; all men must also refrain from donating sperm during the trial and for 6 months after receiving the last dose of GEN1053.

For Monotherapy Dose Escalation (phase 1a) and Combination therapy Dose Escalation (phase 1b) only:

12. Subjects with histologically or cytologically confirmed non-CNS solid tumors that are metastatic or advanced.
13. Subjects who have progressed on standard of care therapy or for whom there is no available standard therapy likely to provide clinical benefit, or who are not candidates for available therapy or who have previously refused available therapy, and for whom experimental therapy with GEN1053 or GEN1053+IM may be beneficial, in the opinion of the investigator.
14. Biopsies for Monotherapy Dose Escalation and Combination therapy Dose Escalation (Table 1-3 and Table 1-7):
    a. All subjects must provide a fresh biopsy. A fresh biopsy is defined as being taken after failure/stop of last prior treatment and within 6 months prior to C1D1.
    Note: Documentation of fresh 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.

b. All subjects should provide an FFPE archival tissue sample from the latest available archival tumor tissue, if available.

c. Local results from the most recent PD-L1 test should be provided prior to enrollment, if available.

For the Expansion part only:

15. Subjects with histologically or cytologically confirmed diagnosis of recurrent, unresectable, or metastatic HNSCC or metastatic NSCLC, who do not have any further available standard therapy or who are not candidates for standard therapy or who have previously refused standard therapy (if subjects had access), and for whom experimental therapy with GEN1053 (HNSCC) or GEN1053+IM (NSCLC, HNSCC crossover) may be beneficial, in the opinion of the investigator.
16. Subjects must meet the following criteria in the respective Expansion cohorts:

For Expansion Cohort 1 (MoA cohort, HNSCC) GEN1053 with crossover to GEN1053+IM:

a. Subjects with recurrent, unresectable, or metastatic HNSCC (with no surgery or RT options) of the oral cavity, pharynx, or larynx who have received up to 3 prior systemic treatment regimens for recurrent, unresectable, or metastatic disease with radiographic PD on or after last prior treatment (maintenance treatment is considered part of one treatment line).

b. Subjects must have received prior platinum-based therapy or alternative chemotherapy if platinum ineligible (eg, a gemcitabine-containing regimen).

c. Subjects must have received 1 prior treatment with a PD-1/PD-L1 inhibitor alone or in combination with other therapy and must have had radiographic PD on or within 6 months after treatment.
Note: Subject must have received at least 2 doses of a PD-1/PD-L1 inhibitor.
Note: For the subjects whose most recent anticancer therapy contained a PD-1/PD-L1 inhibitor, their recent evidence of PD must be confirmed by a second radiographic assessment at least 4 weeks from the date of the initial radiologically documented PD.

d. HPV p16 test results available per local standard of care for subjects with oropharyngeal disease, if available.
Note: Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as by convention these tumor locations are assumed to be HPV negative.

e. Biopsies for Expansion Cohort 1 (Table 1-11):

   i. All subjects must provide a fresh biopsy. A fresh biopsy is defined as being taken after failure/stop of last prior treatment and within 6 months prior to C1D1.
   Note: Documentation of fresh 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.

   ii. All subjects should provide an FFPE archival tissue sample from the latest available archival tumor tissue, if available.

f. Local results from the most recent PD-L1 test should be provided prior to enrollment, if available.

For Expansion Cohort 2 (NSCLC) GEN1053+IM:

g. Subjects with metastatic NSCLC who have received up to 3 prior systemic treatment regimens for metastatic disease with radiographic PD on or after last prior treatment (maintenance treatment is considered being part of 1 treatment line).

i. NSCLC tumors of any histology may be enrolled. Subjects with mutations in KRAS, BRAF, MET genes or RET gene rearrangements or NTRK1/2/3 gene fusions in their tumors may only be enrolled after prior treatment with targeted therapy/standard of care options. Subjects with drug-sensitizing mutations in EGFR or ALK or ROS1 rearrangements are not eligible. Documentation of genomic status should be available per local assessment.
Note: For subjects with squamous NSCLC histology, molecular testing for genomic alterations will not be required.

h. Subjects must have received prior platinum-based therapy or alternative chemotherapy if platinum ineligible (eg, a gemcitabine-containing regimen).

i. Subjects must have received 1 prior treatment with a PD-1/PD-L1 inhibitor alone or in combination with other therapy and must have had radiographic PD on or within 6 months after treatment.
Note: Subject must have received at least 2 doses of a PD-1/PD-L1 inhibitor.
Note: For the subjects whose most recent anticancer therapy contained a PD-1/PD-L1 inhibitor, their recent evidence of PD must be confirmed by a second radiographic assessment at least 4 weeks from the date of the initial radiologically documented PD.

j. Biopsies for Expansion Cohort 2 (Table 1-18)

   i. All subjects must provide a fresh biopsy. A fresh biopsy is defined as being taken after failure/stop of last prior treatment and within 6 months prior to C1D1.
   Note: Documentation of fresh 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.

   ii. All subjects should provide an FFPE archival tissue sample from the latest available archival tumor tissue, if available.

k. Local results from the most recent PD-L1 test should be provided prior to enrollment, if available.

5.2 Exclusion Criteria

Any potential subject who meets any of the following 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.
    b. Symptomatic congestive heart failure (Grade III or IV as classified by the New York Heart Association), unstable angina pectoris, or cardiac arrhythmia.
    c. Uncontrolled hypertension defined as systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥100 mm Hg, despite optimal medical management.
    d. Prolonged QTc interval at baseline of ≥470 milliseconds using Fridericia's QT correction formula.
    e. 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 required only hormone replacement.
    f. 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.
    g. Prior history of myositis, Guillain-Barré syndrome, or myasthenia gravis of any grade.
    h. History of chronic liver disease or evidence of hepatic cirrhosis.
    i. Evidence of interstitial lung disease.
    j. Ongoing pneumonitis or history of non-infectious pneumonitis that has required steroids.
    k. 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 trial treatment.
    l. Serious, non-healing wound, skin ulcer (of any grade), or bone fracture.
    m. Known platelet function defects or a known history or high risk of bleeding events requiring transfusions or hospitalizations unless approved by sponsor.
2. All subjects should undergo a CT scan or MRI of the brain to document new or existing CNS lesions. Any subject with history of intracerebral arteriovenous malformation (shunts), cerebral aneurysm, spinal cord compression (from disease), carcinomatous meningitis, or stroke will be excluded.
    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).

3. Prior therapy:
    a. Radiotherapy within 14 days prior to first trial treatment administration. Palliative radiotherapy will be allowed.
    b. Treatment with an anticancer agent (within 28 days or after at least 5 half-lives of the drug, whichever is shorter), prior to trial treatment administration.
    c. 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.
    d. 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.
    e. Has received any investigational agent (including investigational vaccines) or used an invasive investigational medical device within 28 days before the planned first dose of trial treatment or is currently enrolled in an interventional trial.
    Note: A subject who is in the follow-up phase of an interventional trial may participate if the subject has not received the investigational agent within 28 days of the first dose of trial treatment.
    f. Prophylaxis with live, attenuated vaccines within 28 days prior to first dose of trial treatment; or prophylaxis with the first and/or subsequent injection(s) of SARS-CoV-2 nucleic acid vaccine within 28 days prior to first dose of trial treatment.
    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.
    g. Has received G-CSF or GM-CSF support within 2 weeks prior to first trial treatment administration or is chronically transfusion dependent.
    h. History of ≥ grade 3 allergic reactions to monoclonal antibody therapy or known or suspected allergy or intolerance to any agent to be given during the course of this trial.
    i. Prior treatment with a CD27-targeting agent

j. **Only for Expansion part:** Discontinued treatment due to PD within the first 6 weeks of a CPI-containing treatment.

k. Prior treatment with a T-cell agonist or a CTLA-4–targeting agent within 12 weeks prior to the initiation of trial treatment.

l. Prior treatment with an anti-PD-1/PD-L1 targeting agent within 6 months prior to the initiation of trial treatment.

4. Toxicities from previous anticancer therapies that have not resolved to baseline levels or to grade 1 or less with the exception of alopecia, anorexia, vitiligo, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy. Anorexia, hyperthyroidism, hypothyroidism, and peripheral neuropathy must have recovered to ≤ grade 2.
5. Known past or current malignancies 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 prostate-specific antigen level <0.1 ng/mL.
   e. Any curable cancer with a complete response of >2 years duration.
6. Known allergies, hypersensitivity, or intolerance to trial treatments (including its excipients).
7. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject or that could prevent, limit, or confound the protocol-specified assessments.

   7FR. France: See Appendix 9 for requirements per local health authorities.
8. 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: A subject with a planned surgical procedure to be conducted under local anesthesia may participate.
9. Known history of seropositivity for human immunodeficiency virus.
   Note: HIV testing is required at screening only if required per local health authorities or institutional standards.
10. Known history/positive serology for hepatitis B (unless immune due to vaccination or resolved natural infection or unless passive immunization due to immunoglobulin therapy):
    a. Positive test for antibodies to hepatitis B core antigens

       and

    b. Negative test for antibodies to hepatitis B surface antigens.
11. Known medical history or ongoing hepatitis C infection that has not been cured.
    Note: Hepatitis C testing is required at screening only if required per local health authorities or institutional standards.

12. 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.
13. Has been dosed before in this trial.
14. Is pregnant or breastfeeding and cannot discontinue breastfeeding for the duration of the trial or at least 6 months after the last trial treatment administration or intends to conceive children within 6 months of ending trial treatment.

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.

Individuals who do not meet the criteria for participation in this trial (screen failures) may be rescreened once. The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised. All eligibility criteria must be reassessed at the rescreening visit. Results from assessments performed during the previous screening period are acceptable for rescreening purposes if performed within the specified time frame and the inclusion/exclusion criteria are met.

A new unique subject identifier will not be allocated to the subject at rescreening. Rescreened subjects will be required to sign a new ICF if updates have been made since signing the most recent ICF.

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).

GEN1053 will be administered by qualified site personnel as IV infusion over a minimum of 60 minutes on Day 1 of each treatment cycle of 21 days (Q3W) after all procedures and assessments have been completed.

In the **Dose Escalation phases 1a or 1b,** subjects will be administered GEN1053 according to DLs outlined in Section 4.2.1. In the **Expansion part**, subjects will be administered the RP2D(s) from Dose Escalation phase 1a or 1b for either GEN1053 monotherapy or combination therapy, respectively.

Infusion times and recommendations may be adjusted by the sponsor in consultation with investigators, based on emerging safety information from the Dose Escalation phases. Such changes will be documented in the SC meeting minutes. 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.

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

Trial treatment should be administered as described in Table 6-1 for IMPs. Further details on any AMPs will be provided in a substantial amendment before initiating phase 1b or phase 2a of the trial. Detailed dosing modification guidance is provided in Section 6.7. Information regarding prior and concomitant therapy is provided in Section 6.6.

Table 6-1 Investigational Medicinal Product

	GEN1053[a,b]	**IM[a,b]**
Schedule	Day 1 of each cycle (Q3W)	TBD
Cycle length	3 weeks	TBD
Strength	20 mg/mL	TBD
Dosage formulation	concentrate for solution for infusion	TBD
Route of administration	IV	TBD
Dosing instructions	Refer to IMP Manual	TBD

IM=immunomodulator; IMP=investigational medicinal product; IV=intravenous(ly); Q3W=every 3 weeks; TBD=to be determined (once the IM has been selected).
a. Refer to the IMP Manual for further details.
b. Refer to Appendix 9 for EU authorization status.

6.1.1 Physical Description of Trial Drug(s)

6.1.1.1 GEN1053

GEN1053 is a clear to opalescent, colorless to slightly yellow solution supplied as concentrate for solution for infusion to be diluted (at site).

GEN1053 is supplied in a vial containing 5 mL (100 mg/vial).

GEN1053 will be manufactured and provided under the responsibility of the sponsor.

Refer to the individual IBs for a list of excipients.

6.1.1.2 Immunomodulator

Details will be provided with an amendment before initiating phase 1b.

6.1.2 Packaging

GEN1053 and IM will be packed to meet the applicable regulatory requirements. For further information see IMP Manual.

6.1.3 Labeling

GEN1053 and IM labels will contain information to meet the applicable regulatory requirements. For further details see the GEN1053 and IM IMP Manuals.

6.2 Product Complaint Handling

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 the trial-site personnel within 24 hours of awareness 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 8.4.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Preparation, Handling, and Storage

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

6.3.2 Drug Accountability and Destruction

The investigator or designee must maintain an accurate record of received, returned, and/or destroyed trial treatment supplied by the sponsor and administration of trial treatment to trial subjects in a drug accountability log/record. Drug accountability will be verified on a continuous basis by the site monitor during site monitoring visits and at the completion of the trial. For trials using IRT, drug accountability will be documented within the system.

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

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Subject Numbering

After signing the ICF, subjects will be assigned a unique subject identifier before undergoing any screening procedure(s). Subjects that meet all of the eligibility criteria may be treated.

6.4.2 Treatment Assignment

This is an open-label trial; therefore, blinding of treatment will not be performed. Randomization will not be used in the Dose Escalation part of this trial.

6.4.3 Emergency Unblinding of Treatment Assignment

Not applicable

6.5 Compliance

Trial treatment will be administered by site personnel to assure compliance with trial requirements. The date and time of each trial treatment administration will be documented.

Intervention start and stop dates, including dates for trial treatment delays and/or dose reductions (if applicable) will also be documented.

6.6 Prior and Concomitant Therapies

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

6.6.1 Prior Anticancer Therapies

Prior anticancer therapies received from the time of initial diagnosis until the first dose of trial treatment for the treatment of malignant solid tumors in the Dose Escalation phases 1a and 1b and HNSCC and NSCLC in the Expansion (including surgery, RT, chemo-radiotherapy, systemic treatment regimens, etc) must be documented.

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

Refer to Section 6.6.3.2 for details regarding prohibited prior anticancer therapies or wash-out periods for prior anticancer therapies.

6.6.2 Other Prior Therapies

Any other 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 6.6.3.2 for details regarding prohibited prior therapies or wash-out periods for prior therapies.

6.6.3 Concomitant Therapies

All concomitant medications received within 28 days prior to the first dose of trial treatment and up to 60 days after the last dose of trial treatment should be recorded. All concomitant medications administered during SAEs are to be recorded. All the concomitant medication will be recorded on the eCRF including all prescription, over-the-counter products, herbal

supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

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 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 60 days after the last dose of trial treatment) must be documented.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "prohibited" (Section 6.6.3.2).

Concomitant therapies should also be documented beyond the safety follow-up period only in conjunction with worsening of AEs or new SAEs related to trial treatment.

6.6.3.1 Permitted Concomitant Medications and Therapies

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

- 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 ≥ grade 3 neutropenia, when clinically indicated or at the investigator's discretion. In case of recurring ≥ 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 6.7.2). 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.

- SARS-CoV-2 vaccine is generally permitted, including mRNA-based, protein-based, or non-replicating viral vector-based vaccines. 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.

The trial site will supply supportive medication, eg, premedication, and antiviral medication.

6.6.3.2 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.

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

The following medications and substances are prohibited during 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.
  Note: Seasonal influenza vaccines are generally killed virus vaccines and are permitted; however, intranasal influenza vaccines are live attenuated and are not allowed.

Treatment with bisphosphonates (eg, pamidronate, zoledronic acid, etc) and RANK-L inhibitors initiated within 28 days before the first planned trial treatment dose 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 GEN1053. Caution should be used regarding the use of herbal medications as there may be unknown interactions with trial treatment. Discontinuation of the use of herbal medications prior to trial enrollment is encouraged.

If a subject receives any of the aforementioned prohibited treatments for any reason, the sponsor must be notified for evaluation of whether the subject can continue treatment in the trial.

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 Dosing Modifications

6.7.1 Dose-Limiting Toxicity

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. The DLT evaluation period is defined as 21 days from the first dose of trial drug, ie, Cycle 1 in the Dose Escalation phase 1a (monotherapy) or phase 1b (combination therapy) of the trial. During the DLT evaluation period, the occurrence of any of the toxicities listed below, which are assessed as related to trial treatment, will be considered DLTs..

Toxicities will be graded for severity according to the NCI-CTCAE, version 5.0. CRS will be evaluated according to the ASTCT criteria (Lee et al., 2019).

General

- All grade 5 events
- Grade 4 anaphylaxis
- Grade 4 IRRs

Hematological events

- Grade 4 neutropenia (ie, ANC $<0.5\times10^9$ cells/L [<500/µL]) for minimal duration of 7 days
- Grade 3 and grade 4 febrile neutropenia (ie, ANC $<1.0\times10^9$ cells/L with a single temperature of >38.3 °C [100.9 °F] or with a sustained temperature of ≥38 °C [≥100.4 °F] for more than 1 hour)
- Grade 4 thrombocytopenia ($\leq25.0\times10^9$ platelets/L [<25,000/µL])
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 anemia

Non-hematological events:

- Grade 4 AST, ALT, or bilirubin elevation.
- Grade 3 AST, ALT, or bilirubin elevation that does not recover to ≤ grade 1 within 14 days.
- AST or ALT elevations ≥ grade 2 with concomitant bilirubin >2.0×ULN with no signs of cholestasis, ie, a Hy's law case.
- Any grade 4 irAE.

- Grade 3 irAEs that do not improve to ≤ grade 1 within 7 days by appropriate care or with corticosteroids except for:
    - Grade 3 pneumonitis, which always qualifies as a DLT.
    - Grade 3 nephritis (defined as inflammation of the kidney affecting the structure associated with grade 3 creatinine increase), which always qualifies as a DLT.
- Grade 4 CRS
- Grade 3 CRS which has not resolved to ≤ grade 2 within 48 hours following adequate intervention (including repeated anticytokine therapy)
- Any other ≥ grade 3 nonhematological AE (including liver toxicities other than increases of transaminases and bilirubin), which occurs during the first GEN1053 treatment cycle ***excluding***:
    - Grade 3 fever (>40.0 °C) for ≤ 24 hours.
    - Grade 3 hypotension (resolving to baseline or ≤ grade 1 within 24 hours).
    - Grade 3 IRRs that resolve to ≤ grade 1 within 24 hours.
    - Grade 3 anorexia when grade 2 anorexia was present at baseline or that lasts for <14 days after the last trial treatment 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

The investigator must notify the medical monitor immediately of a DLT. Frequent laboratory monitoring of CBC including differential count 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 GEN1053 or GEN1053+IM related AEs will be monitored and included in the evaluation of the toxicity profile of GEN1053 or GEN1053+IM unless the event is clearly determined to be unrelated to trial treatment (eg, PD).

Subjects experiencing a DLT within the DLT evaluation period should discontinue trial drug 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, and consultation of the DMC may be considered.

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 GEN1053 and/or IM must be agreed between the sponsor and the investigator.

6.7.2 Dosing Modification Guidance and Stopping Criteria

6.7.2.1 Dose Delays and Interruptions for GEN1053 or GEN1053+IM

The methodology for dose escalation is provided in Sections 4.2.1 and 4.2.2.

No intrasubject dose de-escalation will be allowed. The doses of GEN1053 or IM cannot be reduced but may be delayed.

- Administration of trial treatment can be delayed for up to 21 days (ie, 1 cycle) unless otherwise approved by the sponsor medical monitor. If the severity resolves to ≤ 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 GEN1053 or GEN1053+IM, 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. The sponsor may also consult the DMC as specified in Appendix 1.
    - A subject who experiences the same AE of ≥ grade 3 with rechallenge of GEN1053 or GEN1053+IM must discontinue trial treatment immediately.
- For subjects receiving GEN1053+IM combination therapy, both GEN1053 and IM should be withheld or discontinued. Subjects may only continue GEN1053 or IM monotherapy if approved by the sponsor.

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 6-2. The investigators are encouraged to contact sponsor in case of any safety concern that needs thorough discussion and evaluation.

Note that specific rules apply for irAEs, thrombocytopenia, neutropenia, CRS, and IRRs (see Sections 6.7.2.2 and 6.7.2.3).

Table 6-2 Dosing Modification and Management of Treatment-Related AEs

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. If thrombocytopenia ≥ grade 2 is identified, with or without bleeding, further treatment should be interrupted (see Section 6.7.2.3).
Grade 3 (Severe)	Y	Withhold treatment until resolution to ≤ grade 1 or baseline
Grade 4 (Life-Threatening)	Y	Permanent discontinuation except if approved by medical monitor. If continuing on treatment, toxicity must resolve to grade 1 or baseline.

AE=adverse event; N=no; Y=yes.
For recurrent treatment-related AEs upon rechallenge, please see guidance in text.

6.7.2.2 Toxicity Management for Immune-Related AEs

AEs associated with GEN1053 or GEN1053+IM 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 CCI . Guidance for dose modification and management of irAEs is provided in Table 6-3. For additional guidance on the recommended management of irAEs, please refer to the CCI [redacted]

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 6-3).
- Corticosteroid taper should be initiated upon AE improving to grade 1 or less - continue to taper over at least 4 weeks.
- GEN1053 or GEN1053+IM may be resumed after the AE has resolved to ≤ 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 6-3.
- For > grade 1 irAEs, withhold treatment until resolution to ≤ grade 1 unless otherwise specified in Table 6-3.
- 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 6-3 for details).

Table 6-3 Dosing Modification and Management of Immune-Related Adverse Events

Immune-Related AEs	Toxicity Grade (CTCAE v5.0)	Dose Modification	Guidance for Management of irAEs
Pneumonitis	Grade 1	Withhold treatment or proceed with close monitoring.	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 1-2 mg/kg.
	Grade 2	Withhold treatment until 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 1-2 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. For AST or ALT elevations ≥ grade 2 with concomitant bilirubin >2.0×ULN with no signs of cholestasis, ie, a Hy's law case, permanently discontinue.
	Grade 3 or symptomatic	Permanently discontinue if symptomatic Withhold treatment until resolution to ≤ grade 1 and corticosteroid has been tapered - If the grade 3 AST, ALT, or bilirubin increase resolves to ≤ grade 1 within 14 days, trial treatment may be continued after sponsor medical monitor approval	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 ≤ grade 1.

Immune-Related AEs	Toxicity Grade (CTCAE v5.0)	Dose Modification	Guidance for Management of irAEs
		- If the grade 3 AST, ALT, or bilirubin increase does NOT resolve to ≤ grade 1 within 14 days, permanently discontinue trial treatment	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. For ≥ 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.
	Grade 2	Withhold treatment until resolved to baseline[a]	
	Grade 3-Grade 4	Permanently discontinue	
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.
	Grade 3	Withhold treatment until resolved to ≤ grade 1[a]	
	Grade 4	Permanently discontinue	

Immune-Related AEs	Toxicity Grade (CTCAE v5.0)	Dose Modification	Guidance for Management of irAEs
			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.
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; CTCAE=Common Terminology Criteria for Adverse Events; irAE=immune-related adverse event; SJS=Stevens-Johnson syndrome; T1DM=type 1 diabetes mellitus; TEN=toxic epidermal necrolysis; TSH: thyroid-stimulating hormone.

a. The next dose of trial treatment can maximally be delayed 21 days unless approved otherwise by the sponsor medical monitor. If irAE resolves within 21 days to baseline, restart treatment at the same dose level after consulting the sponsor medical monitor.
b. Investigator must contact the sponsor to discuss whether the subject should be withdrawn from trial 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 Appendix 1.
c. For subjects with grade 3 or 4 immune-related endocrinopathy leading to withholding of trial treatment dosing, treatment may be resumed when the AE recovers to ≤ grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).
d. Refer to CCI reference for guidance on immune-related musculoskeletal, nervous system, hematologic, cardiovascular, ocular and specific cutaneous toxicities.

Attribution of Toxicity

When GEN1053 is administered in combination with IM (GEN1053+IM), attribution of an AE to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to GEN1053, IM or both for AEs listed in Table 6-3, both treatment with GEN1053 and IM must be withheld according to the recommended dosing modifications in Section 6.7.2.1.

If the toxicities do resolve and conditions are aligned with what is defined in Table 6-3, GEN1053+IM combination therapy may be restarted at the discretion of the investigator. Reinitiation of either GEN1053 or IM as monotherapy may only be considered after communication with and approval by the sponsor.

6.7.2.3 Dosing Modification for Specific Adverse Events With GEN1053 or IM

Thrombocytopenia Related to GEN1053

The following guidelines should be followed for GEN1053-related thrombocytopenia:

- If thrombocytopenia ≥ grade 2 is identified, with or without bleeding, further treatment must be interrupted.
- If grade ≥ 2 thrombocytopenia fails to resolve to grade ≤1 within 21 days after the planned dosing date, the subject is to discontinue trial treatment unless approved otherwise by the sponsor. Per protocol, observation procedures and assessments will continue until the subject withdraws from the trial or starts another course of systemic anticancer therapy.
- Retreatment may be considered if thrombocytopenia resolves to grade ≤1 within 21 days after the planned dosing date. The sponsor and investigator will discuss any safety concerns in order to decide whether the next cycle should be administered at the same schedule or whether the dosing interval in subsequent cycles should be increased.
- If the retreatment results in grade ≥2 thrombocytopenia, the next administration of trial treatment should be delayed for up to 21 days until the toxicity has resolved to grade ≤1. The sponsor and investigator will discuss any safety concerns in order to decide whether next cycle should be administered at the same schedule or whether the dosing interval in subsequent cycles should be increased.
- If more than 2 dose interruptions occur due to grade ≥2 thrombocytopenia, trial treatment will be discontinued. Per protocol, observation procedures and assessments will continue until the subject withdraws from the trial or starts another course of systemic anticancer therapy.
- Trial treatment must be prematurely discontinued if the subject experiences grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding. For subjects with platelet count $<50\times10^9$/L, aspirin or other concomitant medications with effect on platelet function or coagulation should be paused. For subjects with severe, persistent thrombocytopenia potentially related to GEN1053, it is recommended to perform a bone marrow biopsy.

Bleeding:

Subjects with any bleeding symptoms, even mild, (eg, unjustified bruising, purpura, petechiae, epistaxis or gingival bleeding) will be instructed to contact the site immediately. Lab tests must be drawn to assess hematological parameters including platelets in case of signs of bleeding. Importantly, ≥ grade 3 thrombocytopenia and ≥ grade 2 bleeding events need to be reported within 24 hours irrespective of event seriousness (see Section 8.4.3).

- For any clinically significant bleeding event, supportive care may be provided following local guidelines. For significant bleeding associated with thrombocytopenia of ≥ grade 2, platelet transfusions, high-dose corticosteroids or immunoglobulin therapy should be considered according to local standards.

Neutropenia and Febrile Neutropenia Associated With GEN1053 or IM Administration

Table 6-4 Dosing Modification and Management of Neutropenia and Febrile Neutropenia

CTCAE Term	Toxicity Grade (CTCAE v5.0)	Dose Modification	Guidance for Management of AE
Neutropenia or Febrile neutropenia	Grade 3 or Grade 4	Withhold treatment until resolution to ≤ grade 1	Administer colony-stimulating factors including G-CSF, pegylated G-CSF, or GM-CSF according to Institutional standards. For grade 3 or 4 neutropenia occurring in Cycle 1, grade 3 or 4 neutrophil count must be observed in 2 consecutive assessments at least 12 hours apart without improvement prior to administration of growth factors.

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

Cytokine Release Syndrome Related to GEN1053 or IM

In the unexpected case an event of CRS occurs, grading of the CRS 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 event or a cytokine blockade-refractory grade 3 CRS 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 GEN1053, are not available and potential events of CRS must be treated symptomatically. Subjects with CRS 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.

Infusion-Related Reactions Associated With GEN1053 Administration

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

- Grade 1: If an IRR grade 1 occurs, the infusion does not need to be interrupted and can be continued at the investigator's discretion at half the infusion rate under close medical supervision.

- Grades 2 to 3: If an IRR grade 2 or 3 occurs, 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 ≤ grade 1 within an hour.

    - Subjects who have experienced prior infusion-related grade 2 or 3 reactions in the trial should be premedicated. Premedication to prevent IRR in subsequent infusions may be administered at the investigator's discretion according to local guidelines but preferably includes an antihistamine (eg, diphenhydramine 50 mg or equivalent antihistamine), acetaminophen/paracetamol (eg, acetaminophen 500-1000 mg or equivalent), and if considered necessary, subjects should receive corticosteroids at a suggested maximum dose of 100 mg prednisone or equivalent.

    - If the subject has a second grade 3 IRR despite premedication, the infusion should be stopped, and the subject should 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 hours after ending infusion of GEN1053. For all subsequent cycles, subjects must be observed for at least 2 hours after ending infusion of GEN1053, unless they have experienced an IRR in any previous cycle. In the latter case, the clinical observation should continue to be 4 hours. Subjects must always be observed for at least 2 hours after ending infusion of IM.

- 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 reported on the concomitant medication page in the eCRF.

6.7.2.4 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 6.7.1) should discontinue trial drug immediately. If requested by the investigator, the sponsor may allow a subject with a DLT to continue in the trial. For this decision, a thorough benefit-risk assessment of the individual subject is required, and consultation of the DMC may be considered.

- 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 GEN1053 and/or IM must be agreed between the sponsor and the investigator.

- If the subject experiences a TRAE that meets the criteria for treatment discontinuation as specified in Sections 6.7.2.2 and 6.7.2.3 and Table 6-3 and Table 6-4.

- An AE that fails to resolve to ≤ grade 1 within 21 days due to a toxicity possibly related to trial drug, unless otherwise approved by the sponsor medical monitor.

- Treatment-related grade 4 or life-threatening AE, except with approval from the medical monitor.

- Second occurrence of an IRR of ≥ grade 3 despite premedication prior to the second infusion.

- First occurrence of anaphylaxis or a grade 4 IRR.

- Subjects with grade 4 transaminase or bilirubin elevation.

- Subjects with abnormal liver function parameters that meet Hy's law criteria as defined in Section 6.7.1.

- In case of thrombocytopenia not resolving to ≤ grade 1 within 21 days after the planned dosing date, unless approved otherwise by the sponsor.

- If the subject experiences grade 4 thrombocytopenia or grade 3 thrombocytopenia with clinically significant bleeding.

- First episode of CRS grade 4.

- First episode of cytokine blockade-refractory grade 3 CRS 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).

6.7.2.5 Safety Stopping Rules for the Trial

The trial can be stopped for unacceptable toxicity based on a risk-benefit assessment after consultation with the DMC. Deaths considered related to GEN1053 will always be assessed by the DMC.

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.

6.8 Treatment of Overdose

6.8.1 Overdose of GEN1053

For this trial, an overdose of GEN1053 is defined as a subject receiving a dose in excess of 10% of that specified in this protocol.

In case of overdose, medication errors, misuse, and/or abuse of GEN1053, subjects should receive supportive care according to local guidelines and potential side effects of GEN1053 should be treated symptomatically.

In the event of an overdose, the investigator should:

- Closely monitor the subject for any AEs/SAEs and laboratory abnormalities.
- Obtain a plasma/serum sample for PK analysis if requested by the sponsor's medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.
- Contact the sponsor's medical monitor immediately (see Section 8.4.3).

6.8.2 Overdose of IM

Further details on the IM will be provided in a substantial amendment before initiating phase 1b of the trial.

6.9 Treatment After the End of the Trial

6.9.1 Subject Contact and Trial Treatment After the End of the Trial

Investigators should attempt to recontact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the ICF (refer to Appendix 1, Informed Consent Process).

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.

7 DISCONTINUATION OF TRIAL TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Trial 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 and unless the subject withdraws consent, 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 7.1.2) and are not considered discontinued from the trial (see Section 7.2), provided that consent for trial participation has not been withdrawn.

A subject's trial treatment must be discontinued for any of the following reasons:

- Unacceptable AE requiring treatment discontinuation (refer to Section 6.7.1 and 6.7.2.4)
- Pregnancy
- 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).
- Death
- Investigator believes that it is in the best interest of the subject to stop GEN1053 or GEN1053+IM treatment
- Subject non-compliance
- Sponsor decision
- Subject request to discontinue trial treatment
- Lost to follow-up (see Section 7.3)
- Termination of the trial by the sponsor

For subjects receiving GEN1053+IM combination therapy, both GEN1053 and IM should be discontinued. Subjects may only continue GEN1053 or IM monotherapy if approved by the sponsor.

Subjects should, whenever possible, irrespective of the reason for discontinuation, be examined as soon as possible and the treatment discontinuation visit should be performed. If the treatment discontinuation visit coincides with a regularly scheduled cycle visit, the treatment discontinuation evaluations will supersede those of the regularly scheduled cycle visit. 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. For subjects crossing over from GEN1053 to GEN1053+IM, re-baseline visit details are provided in Table 1-13.

When a subject discontinues treatment with trial treatment, the subject remains in the trial and is followed until meeting one of the reasons listed in Section 7.2.

In addition, the subject will still be followed for safety (see Section 7.1.1) and survival status (see Section 7.1.2) through the end of the trial.

Subjects should always be followed for safety as detailed in Section 8.4 and Appendix 3.

After trial treatment discontinuation, the subject should receive suitable treatment as decided by the investigator (see Section 6.9).

7.1.1 Safety Follow-up Evaluation

Subjects discontinuing from treatment for any reason will have 2 safety follow-up visits, at 30 days (+5 days) and 60 days (±7 days) after the last trial treatment administration, respectively. If the subject initiates new anticancer treatment within 30 days of the last trial treatment administration, the safety follow-up visit should be performed prior to starting new anticancer treatment. Once new anticancer treatment is initiated, the subject will move into survival status follow-up (see Section 7.1.2).

7.1.2 Survival Status

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. Subjects may be contacted by telephone, email, or visit. Subjects who are not available, or whose designated family members are not available, for this assessment should be entered as “lost to follow-up” (see Section 7.3 and Section 6.8). In the monotherapy dose escalation part, there will be no survival follow-up for the last subject discontinuing treatment.

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 may 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 Subject Withdrawal From the Trial

A subject will be withdrawn from the trial for any of the following reasons:

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

When a subject withdraws before completing the trial, the reason for withdrawal is to be documented.

During both the monotherapy Dose Escalation phase 1a and the combination therapy Dose Escalation phase 1b, subjects who withdraw before the end of the DLT period may be replaced. These replacement subjects will be assigned to the same treatment cohort as the subjects they are replacing.

If a subject discontinues trial treatment and withdraws from the trial before PD, the treatment discontinuation visit assessments should be obtained whenever possible. If the reason for withdrawal 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.

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 Appendix 5 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 efficacy, PK, immunogenicity, pharmacodynamic/biomarker, safety, and other measurements applicable to this trial.

All assessments should be performed prior to trial treatment administration, unless otherwise indicated in the Schedule of Activities.

Blood collections for PK and pharmacodynamic assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the participation in the trial.

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

8.1 Demography and Baseline Assessments

8.1.1 Demographics

Demographic details will be assessed at screening.

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:

The primary site of cancer, and initial and current disease stage (TNM staging system), will be recorded at screening.

For all subjects, record the PD-L1 status as per local assessment, if available.

For all subjects, record the dMMR or MSI status as per local assessment, if available.

The following should be recorded if available for subjects with the following types of cancer:

- Breast cancer: HER2, ER, and PgR status as per local assessment
- Ovarian: BRCA status as per local assessment
- HNSCC: HPV status in subjects with oropharyngeal disease as per local assessment

- NSCLC: the tumor mutational status including EGFR, ALK, KRAS, BRAF, MET, ROS1 genes or RET gene rearrangements or NTRK1/2/3 gene fusions as per local assessment

- Cervical cancer: HPV status as per local assessment

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

8.1.3 Medical History

Any medical condition (signs, symptoms, and diagnosis) occurring prior to first dose of trial treatment should be documented in the source documents as medical history. Medical conditions that occur after the ICF is signed and prior to first dose of trial treatment should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including wash-out 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 Appendix 3.

Recording of prior therapies are detailed in Section 6.6, selected prior laboratory data 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), Appendix 7).

Importantly, in subjects who discontinue trial treatment without evidence of radiographic PD, tumor imaging must be performed until evidence of radiographic PD.

If the subject withdraws or is lost to follow-up, the data already collected and the data from the end of the trial visit will be kept.

8.2.1 Definition of Target and Nontarget Disease

Up to 5 target lesions (maximum 2 per organ) will be defined at screening and these must be followed throughout the trial. Biopsied tumor lesions or tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered evaluable. For subjects with a single target lesion, it is mandatory to perform the imaging before taking the biopsy (both must be performed during the screening period). Biopsies cannot be taken from this single target lesion on-treatment unless approved by the sponsor medical monitor. Nontarget lesions will also be assessed throughout the trial.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the trial so that the comparison is consistent.

Initial tumor imaging at screening must be performed within 21 days prior to the date of first dose. If a CT scan or MRI has been performed within 21 days prior to visit C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial. Scans that exceed the 21-day window may be used for trial enrollment with sponsor approval. The site must review screening images to confirm the subject has measurable disease per RECIST 1.1.

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. Head and neck imaging is always required for subjects with HNSCC. Imaging of the pelvis is not required for subjects with HNSCC 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 1.1, but only if the CT portion is of similar diagnostic quality to CT alone.

- The same imaging modality and ideally the same scanner should be used throughout the trial to optimize the reproducibility of the assessment and preserve the accuracy of the assessment of response or 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 (-7 days), every 6 weeks (±7 days) for 50 weeks, and every 12 weeks (±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 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 1.1 criteria will be used for secondary endpoint response evaluation (Eisenhauer et al., 2009) and Appendix 7; iRECIST will be used for exploratory endpoint response evaluation (Seymour et al., 2017).

- Additional CT or MRI scans may be performed at the investigator's discretion to confirm response or new symptoms. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. In this case, the investigator must choose the imaging technology based on the clinical indication.
    - 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 growth and possible independent review of disease assessments for subjects enrolled. Images obtained at an unscheduled timepoint should be captured in the eCRF and submitted to the central imaging vendor for subjects enrolled in the Expansion part.
    - 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, efficacy assessments must continue.

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

iRECIST 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 status
- 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 that are clinically unstable are not required to have repeated imaging to confirm PD by iRECIST; however, a confirmation of progression scan may be obtained at the investigator's discretion after consultation with the sponsor.

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

8.3 Clinical Safety Assessments

Details regarding the DMC, DEC, and SC are provided in Appendix 1.

AEs will be reported and followed by the investigator as specified in Section 8.4 and Appendix 3.

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 up by the investigator until resolution or until a clinically stable condition is reached depending on if they correspond to an AE, AESI or an 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 should be performed during screening period. At subsequent visits, a symptom-directed/clinically indicated (brief) physical examination may be performed.

Full Physical Examination:

The investigator or qualified designee will perform a full physical examination according to standard of care at the time points specified in the Schedule of Activities, Section 1.3. After the first dose of trial treatment, new or worsening findings that are considered clinically significant should be reported as AEs.

Brief Physical Examination:

For cycles that do not require a full physical examination (as specified in the Schedule of Activities, Section 1.3), the investigator or qualified designee will perform a symptom-directed physical examination as clinically indicated 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

8.3.2.1 Height

Height (without shoes) must be measured at screening and rounded to the nearest centimeter or inch.

8.3.2.2 Weight

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 or pound.

8.3.3 Vital Signs

Vital signs, including temperature (°C or °F), blood pressure (mm Hg), and heart rate (beats/min) should be measured with the subject in a supine or reclined position and recorded. Subjects should be resting and in a horizontal or half laid 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.

Vital signs will be measured as indicated in the Schedule of Activities (Section 1.3) according to Table 1-4, Table 1-8, Table 1-12, and Table 1-19.

On infusion days, vital signs should be assessed as described in Table 1-4 and Table 1-12 for GEN1053 monotherapy and in Table 1-8 and Table 1-19 for GEN1053+IM combination therapy, respectively.

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).

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 QTc will be calculated using Fridericia's formula:

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

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 the ECG using the paper ECG reading from the ECG machine, and sign and date the printout. In case of discrepancy between central and the investigator ECG readings, 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 (Appendix 6).

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 growth kinetics, if available.

Blood samples for serum chemistry, hematology, and other laboratory tests will be collected as indicated in the Schedule of Activities (see Section 1.3) and further described in Appendix 2, including Table 10-1. 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.

Local laboratory test results should be assessed for abnormalities. 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 (see Appendix 3 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: A CTCAE grade 3 or 4 laboratory result abnormality does not automatically indicate an SAE.

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 Appendix 3.

8.4.1 Definition of Adverse Events and Serious Adverse Events

The definitions of AEs, SAEs, AESIs as well as attribution definitions; severity criteria; special reporting situations; and procedures are provided in Appendix 3.

8.4.1.1 Adverse Events of Special Interest

For GEN1053, the following events have been defined as AESIs, irrespective of relatedness to trial treatment:

- AEs of thrombocytopenia (ie, low PLT counts that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in trial treatment)
- AEs of bleedings

AESIs can be serious or nonserious, as per standard seriousness criteria (Appendix 3). For AESIs requiring expedited reporting, please see Section 8.4.3.5. AESIs defined for treatment with IM will be determined and amended before starting phase 1b.

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 6.7.2.3 for further IRR treatment guidance).

8.4.2 Adverse Event Reporting

As noted in Section 8.1.3, medical conditions (signs, symptoms, and diagnosis) that occur after the ICF is signed and prior to the first dose should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (ie, tumor biopsy and/or CT scan), including wash-out or discontinuation of prior medications.

All other AEs, whether serious or nonserious (see definitions in Appendix 3), will be documented from the first dose of trial treatment until the last safety follow-up visit, subject withdrew consent, subject started new anticancer treatment, or the subject dies, whichever comes first. The safety reporting periods are defined in Table 8-1.

Table 8-1 Reporting Period and Requirements

Trial Period	Reporting Requirements
Signing of ICF until first dose of trial treatment	AEs, if assessed by the investigator to be caused by a protocol-mandated procedure (eg, tumor biopsy, CT scan), including wash-out or discontinuation of prior medications.
First dose of trial treatment through SFU2	All AEs and SAEs (see definitions in Appendix 3), regardless of causality, will be documented.
After SFU2 through end of trial/after end of trial	There is no requirement to monitor subjects for AEs and SAEs following the protocol-required safety reporting periods 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 Appendix 3 for additional guidance for recording and reporting AEs and Section 7.1.1 for timing of safety follow-up visit(s).	

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

For details regarding follow-up of AEs and SAEs and reporting period for SAEs judged as related to GEN1053 and/or IM, see Section 8.4.6. Refer to Section 6.2 for guidance regarding product complaints.

8.4.3 Events Requiring Immediate Reporting

Refer to Appendix 3 for additional guidance for recording and reporting AEs.

8.4.3.1 Second Primary Malignancy

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

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 following:

- The subject visit at which the SAE 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 6.8. 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. 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 trial treatment, 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 in female subjects or partners of male subjects must be reported to the sponsor within 24 hours of knowledge of the event, using the pregnancy reporting paper form available in the investigator site file. 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 the 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

AESIs in this protocol are defined in Section 8.4.1.1.

The following AESIs need to be reported to the sponsor within 24 hours of awareness irrespective of event seriousness:

- Grade 3+ thrombocytopenia (ie, AEs of thrombocytopenia with PLT count less than 50×10^9/L)

- Grade 2+ bleedings (ie, bleeding that requires medical intervention/hematocrit monitoring, as per CTCAE criteria per type of bleeding)
  Note: AEs of grade 1 bleedings and of ≤ grade 2 thrombocytopenia must be reported as per regular AE timelines, depending on whether they fulfill or not any seriousness criterion based on the investigator's assessment.

All AESIs will be closely monitored to timely identify, quantify and qualify any relevance of the nonclinical findings to humans and the adequacy of the mitigation strategies described in Sections 2.3.2, 2.2.2.1, 2.2.3.1 and 6.7.2. All AESIs will be taken into consideration during DEC reviews and SC decisions, regardless of their occurrence (within or outside the DLT period).

8.4.4 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. SUSARs aggregated line listings will be distributed quarterly, or every 6 months, or in periods as warranted for regulatory compliance; 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.

8.4.4.1 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 its progression 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 symptom 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 Appendix 3, under the definition of SAE, for additional reasons when hospitalizations should not be reported as SAEs.

8.4.5.1 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 last safety follow-up visit 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 Warnings and Precautions

Refer to the IB for detailed information for precautions and warnings for GEN1053.

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 as needed.

8.5 Pharmacokinetics

Venous blood samples will be collected for analyzing matrix concentrations of GEN1053 as specified in the Schedule of Activities (Section 1.3). Date and 24-hour clock time of each sample will also be recorded.

Samples collected for GEN1053 PK will be divided into aliquots prior to analysis and may additionally be used to evaluate safety or efficacy aspects to address any concerns that may arise during or after the trial period. Genetic analysis will not be performed on these samples. Subject confidentiality will be maintained.

Samples will be analyzed to determine concentrations of GEN1053 using a validated, specific, and sensitive method by or under the supervision of the sponsor.

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

8.6 Pharmacodynamics

Refer to Section 8.7 for pharmacodynamic biomarkers.

8.7 Biomarkers

8.7.1 Biomarker Sample Collection

Samples for biomarker analyses will be collected as specified in the Schedule of Activities. 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 handling sheets, 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 standard of care. 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.

8.7.2 Biomarker Assessments in Tumor Samples

A fresh biopsy collected before treatment with trial treatment (ie, during the screening period) is required for all subjects for enrollment. This fresh biopsy must not be older than 6 months and taken after failure/stop of last prior treatment, but before treatment with trial treatment. Documentation of fresh 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. The fresh biopsy should be a core biopsy or resected tissue. A fine needle aspirate will not be sufficient. The following specimen types are not acceptable biopsy samples: cytological specimens, aspirates, bone, or bone marrow. All tumor biopsies should be FFPE. A subject must also provide an archival tumor sample, if available. Refer to Section 8.2.1 for additional information on biopsy procedures related to defining target lesions.

During the trial, an on-treatment biopsy is also required, between Cycle 2 Day 8 and Cycle 2 Day 21 (inclusive) of trial treatment; and if any additional tumor biopsies are collected that are part of normal clinical practice, these will also be examined as described below.

Biomarker analyses in tumor samples at baseline and during treatment may help to confirm the GEN1053 or GEN1053+IM MoAs and enable the identification of biomarkers predictive of response to GEN1053 or GEN1053+IM. 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.

8.7.2.1 Protein Expression Analyses

Expression of proteins related to malignant solid tumor biology or GEN1053 and GEN1053+IM MoAs 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.

8.7.2.2 RNA Expression Analyses

RNA sequencing may be performed on tumor biopsies to determine CD27, CCI RNA expression levels, as well as to evaluate other potential genes associated with CD27, CCI biology, with immune effector cell activation, or with cancer biology in general.

8.7.2.3 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 CD27, CCI expression or function, GEN1053 and GEN1053+IM proposed MoAs, or cancer biology in general.

8.7.3 Biomarker Assessments in Blood Samples

Biomarker assessments may also be performed using whole blood samples to investigate potential pharmacodynamic markers and explore the relationship to the efficacy and/or MoA of GEN1053 and GEN1053+IM. Assessments will be performed at baseline (before infusion at Cycle 1 Day 1) and during treatment in order to enable correlation analyses with response to treatment or disease biology.

8.7.3.1 Immunophenotyping Analyses

Immunophenotyping (eg, measurement of T cells, B cells, NK cells, monocytes, DCs) may be performed at baseline and during treatment at planned visits to evaluate changes associated with the MoA of GEN1053 and GEN1053+IM, subject response to GEN1053 and GEN1053+IM, and disease biology. Target engagement may be determined at baseline and during treatment at planned visits to evaluate changes associated with the MoA of trial treatment, DL, and subject response to trial treatment.

8.7.3.2 Cytokine or Soluble Factors Analyses

Cytokine and complement factors (C3a and Bb) analysis may be performed at baseline and during treatment at planned visits to investigate safety and potential pharmacodynamic markers of GEN1053 and GEN1053+IM. sCD27 analysis may be performed at baseline as an exploratory biomarker.

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

cfDNA/RNA, including ctDNA and/or exoRNA, may be measured, and analyses such as RNA expression levels, DNA mutations, copy number variations, microsatellite instability, indels,

and/or rearrangements in genes may be performed to evaluate the association of such biomarkers with GEN1053 and GEN1053+IM MoAs, subject response, or disease biology.

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 genomic biomarker analysis (DNA/RNA).

If DNA/RNA research evaluations are performed, the results may be reported in a separate report.

8.8 Immunogenicity

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

Samples will be screened for ADAs binding to GEN1053 and the titer of confirmed positive samples will be reported. Neutralization characterization of ADAs may also be performed using appropriate methods.

Further details are included in the laboratory manual.

Samples will be collected to evaluate the presence of ADAs against GEN1053 in monotherapy as well as in the combination cohorts. Samples collected for ADAs to GEN1053 in monotherapy as well as in combination therapy, may additionally be used to evaluate safety or efficacy aspects that address any concerns arising during or after the trial period for further characterization of immunogenicity. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

9 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 will be detailed further in the SAP.

The SAP will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All presentations will be done separately for the Dose Escalation part and the Expansion part. Subjects in the Dose Escalation part will typically be analyzed according to the DL received. Subjects in the Expansion part will be analyzed according to their assigned Expansion cohort. Exploratory analyses may be considered for HNSSC subjects crossing over from GEN1053 to GEN1053+IM due to PD.

The main analyses will be timed as follows:

- **Interim analysis, Monotherapy Dose Escalation phase 1a and Combination therapy Dose Escalation phase 1b**: Main safety and pharmacodynamic analyses will be conducted on all subject data at the end of the escalation (upon completion of DLT evaluation of the last subject in the Escalation phase).

- **Primary analysis, Expansion phase 2a**: The Expansion part consists of parallel cohorts, wherein each Expansion cohort may report its individual main analysis. Main safety, pharmacodynamic and efficacy analyses will be conducted at the time all subjects who are still receiving trial treatment have at least 2 postbaseline scans performed (such that the exploratory efficacy endpoints can be assessed) or have completed the safety follow-up period or have ended the trial.

9.1 Statistical Hypotheses

Due to the early stage of this trial, no formal hypothesis testing for confirmative purposes will occur.

9.2 Sample Size Determination

No formal sample size calculation was performed.

In the Dose Escalation and Expansion parts:

- In the Monotherapy Dose Escalation phase 1a: up to 63 (maximum 9 subjects at each DL) subjects who are ≥18 years of age and have malignant solid tumors will be treated.

- In the Combination therapy Dose Escalation phase 1b: up to 27 subjects (maximum 9 subjects in each cohort)

- In the Expansion phase 2a: approximately 80 subjects (approximately 40 for each cohort).

For the Expansion part, a sample of 40 per cohort is deemed enough to provide a preliminary assessment of efficacy. A sample size of 40 subjects would ensure at least 90% power to detect a shift to an ORR of 30% from a base rate of 10% given a 1-sided binomial test at a 5% significance level. In addition, efficacy monitoring will be applied as described in Section 9.5.

9.3 Populations for Analyses

9.3.1 Full Analysis Set

The FAS and safety set are defined in the same way and will comprise all subjects who receive at least 1 dose of trial drug. Subjects will be analyzed according to the actual trial treatment received.

9.3.2 Safety Set

The safety set is equal to the FAS.

9.3.3 Response Evaluable Set

The response evaluable set consists of all subjects who have baseline evaluable disease according to RECIST 1.1 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.

9.3.4 Dose-Determining Set

The DDS will include all FAS subjects in the escalation part who meet the minimum exposure criterion and have sufficient safety evaluations or experience a DLT during the first 21 days of dosing (ie, in Cycle 1).

A subject will meet the minimum exposure criterion if the subject receives at least 80% of the preplanned dose of each trial treatment during the DLT period.

Subjects who do not experience a DLT during Cycle 1 (the first 21 days of dosing) will be considered to have sufficient safety evaluations 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. Subjects will be analyzed according to the trial treatment received, as defined for the FAS.

9.3.5 Pharmacokinetic Analysis Set

The PAS will include all subjects who receive at least 1 dose of trial drug and who provide at least 1 evaluable PK sample for GEN1053 in monotherapy and combination therapy. Refer to Table 1-3, Table 1-6, Table 1-10, Table 1-15 and Table 1-16 for further detail on sampling times.

9.3.6 Immunogenicity Analysis Set

The IAS will include all subjects who receive at least 1 dose of GEN1053 as monotherapy or combination therapy and have a baseline and at least 1 evaluable on-treatment (predose) ADA sample for GEN1053 as monotherapy or combination therapy.

9.4 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 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.

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

9.4.1 Subject Demographics and Baseline Characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively for all subjects, by dose cohort and by indication in Expansion for the FAS.

Relevant medical histories and current medical histories at baseline will be summarized separately by system organ class and/or preferred term, (for all subjects, by dose cohort, and by indication in Expansion).

9.4.2 Efficacy

9.4.2.1 Antitumor Activity Based on RECIST 1.1

RECIST criteria (v1.1) will be used to define response (Eisenhauer et al., 2009). Additional details of RECIST can be found in Appendix 7.

The BOR is the best response recorded from the start of the treatment until PD/recurrence (the smallest measurements recorded will be used as the reference for PD). Subjects with CR or PR are considered to be objective responders. Subjects with CR, PR, or SD are considered to be in disease control. Subjects for whom data are NE are counted as nonresponders.

The best change (maximal reduction in the sum of the diameters in the target lesions) in target lesions at any time on trial will be reported using waterfall plots.

Individual subject data listings and summaries of objective response, best overall tumor response, and disease control will be presented by dose cohort/indication and total.

9.4.2.1.1 Objective Response Rate

The confirmed ORR is defined as the proportion of subjects with BOR of confirmed CR or confirmed PR (ie, “responders”), as per local review and according to RECIST v1.1. Repeat imaging may be performed no less than 4 weeks after the criteria for CR or PR are met to confirm the initial response.

An assessment of SD requires at least 5 weeks from C1D1 to scan date.

9.4.2.1.2 Duration of Response

DoR only applies to subjects whose confirmed BOR is CR or PR and is defined as the time from the first documentation of objective tumor response (CR or PR) to the date of first PD or death due to any cause.

DoR will be censored and summarized in the same way as PFS, see below.

9.4.2.2 Exploratory Objectives

9.4.2.2.1 Biomarkers

Biomarker analyses in this trial are exploratory and focused on confirming the MoA of GEN1053, identifying potential PD markers to help identify the appropriate dose and schedule of GEN1053, and identifying potential predictive markers that may be further validated in prospective trials with GEN1053.

Expression of biomarkers, such as CD27, CCI on peripheral immune cell populations, as well as cytokine measurements, will be tabulated for all subjects who have samples collected and testing performed. Biomarker assessments will be summarized by time point using descriptive statistics. Changes in biomarker parameters, as compared to baseline, will be calculated and analyzed for association with relevant clinical endpoints such as objective response, PFS, and OS. Subgroup analyses may be performed to evaluate differences between biomarker parameters in groups of responders and nonresponders or other clinically relevant subgroups, and to evaluate the associations between biomarker parameters and specific clinical endpoints. Univariate and multivariate analyses, as well as pathway analyses, may also be performed if applicable. Any pharmacodynamic measures will be listed, tabulated, and plotted as appropriate. Subjects may be grouped by cohort, dose schedule, or clinical response. Further details will be provided in the SAP.

Results of biomarker analyses may also be presented in a separate report.

9.4.2.2.2 Antitumor Activity Based on iRECIST

Responses assigned using iRECIST (NCCN, 2021a; Seymour et al., 2017) have a prefix of "i" (eg, iCR or iPR, and iUPD or iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for iSD, iPFS, iDoR, iDCR, and iORR.

The exploratory analysis methodology is similar to that described in Section 9.4.2.1.

9.4.2.2.3 Progression-Free Survival

PFS is defined as the time from the date of C1D1 to the date of the first documented PD or death due to any cause. PFS will be assessed via local review according to RECIST v1.1 (Eisenhauer et al., 2009). PFS will be censored in accordance with Table C1 in Appendix C in the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-small Cell Lung Cancer Drugs and Biologics (FDA, 2015).

PFS will be analyzed in the FAS population. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, and 95% CIs of the medians will be presented for each Expansion cohort.

9.4.2.2.4 Overall Survival

OS is defined as the time from date of C1D1 to date of death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cutoff date).

The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, first and third quartiles, and 95% CIs of the medians will be presented for each Expansion cohort.

9.4.2.2.5 Tumor Growth

Prebaseline scans will be collected to explore tumor growth and selected, concomitant prebaseline laboratory data (neutrophils, lymphocytes, platelets, hemoglobin, albumin, and LDH) will be collected to explore their association with tumor growth prior to treatment, and to evaluate drug effect on tumor growth. For this analysis, scans will be centrally read to ensure a consistent reading of prebaseline and on-treatment scans. These central readings will only be used to evaluate the prebaseline and on-treatment change in tumor size based on target lesions. The response to treatment described in Section 9.4.2.1 will be based on investigator readings. The results of this exploratory analysis will be reported in a separate report.

9.4.3 Safety

9.4.3.1 Adverse Events

For all safety analyses, the FAS (which is identical to the safety set) will be used.

The overall observation period will be divided into 3 mutually exclusive segments:

1. Pretreatment period: from day of subject's informed consent to the day before first dose of trial medication

2. On-treatment period: from day of first dose of trial medication to 30 days after last dose of trial medication

3. Posttreatment period: starts when the on-treatment period ends

Summary tables for AEs will include only AEs that started or preexisting AEs that worsened during the on-treatment period (ie, TEAEs).

The incidence of TEAEs (new or worsening from baseline) will be summarized by system organ class and/or preferred term; intensity (based on grades of NCI-CTCAE version 5.0) (see Section 8.4.1); type of AE; relationship to each trial treatment.

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

All deaths (on-treatment and posttreatment) will be summarized.

All AEs, fatal AEs, AESIs, and SAEs (including those from the pre- and posttreatment periods) will be listed and those collected during the pretreatment and posttreatment period will be flagged.

Further summaries of AEs will be specified in the SAP.

9.4.3.2 Clinical Laboratory Tests

Grading of laboratory values will be assigned programmatically as per NCI-CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be considered.

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

9.4.3.3 Other Safety Data (eg, Vital Signs, ECG Parameters)

The following will be provided, as necessary.

- ECOG-PS will be summarized.
- Abnormal findings in physical examinations will be summarized.
- 12-lead ECGs including PR, QRS, QT, heart-rate-corrected QTcF, and RR intervals will be obtained for each subject during the trial. ECG data will be read and interpreted centrally in the Dose Escalation phase only. Any relationship between QTcF and PK concentrations across DLs and time points will be investigated.
- Vital signs data will be tabulated and listed; notable values may be flagged.

9.4.3.4 Patient-Reported Outcomes

Not applicable

9.4.4 Pharmacokinetic Analyses

Individual curves of concentration of GEN1053, including information on actual dose, will be presented for all subjects. All available data will be shown in these figures. PK parameters will be calculated based on noncompartmental methods as specified in Table 9-1. These PK parameters will be calculated separately for the Cycle 1 and Cycle 3 administrations. C_{max}, t_{max}, and predose values will be summarized and presented graphically for all trial days where measured.

The relationship between derived PK parameters and covariates such as actual dose, weight, and selected laboratory parameters will be evaluated graphically.

Descriptive statistics of PK endpoints will include arithmetic and geometric means, standard deviation, %CV, median, minimum, and maximum.

Missing concentration values will be reported as is in data listings. Concentration values below LLOQ will be handled as LLOQ/2 in summary statistics and reported as is in data listings. Any missing PK parameter data will not be imputed.

Further exploratory analyses of PK data may be performed.

Table 9-1 Noncompartmental Pharmacokinetic Parameters

CL	The total body clearance of drug from the plasma
V	Volume of distribution
$t_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi-logarithmic concentration-time curve
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration
C_{trough}	The minimum observed plasma, blood, serum, or other body fluid drug concentration prior to the subsequent dose.
t_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration
AUC_{tau}	The AUC from time zero to day 21 (mass × time × volume -1)
AUC_{last}	The AUC from time zero to last quantifiable measurement

9.4.5 Pharmacodynamic Analyses

Please see Section 9.4.6.

9.4.6 Biomarker Analyses

The exploratory biomarker assessments are intended to evaluate potential pharmacodynamic and safety biomarkers, and to identify markers predictive of response or resistance to GEN1053 as monotherapy or in combination with IM. Since this clinical trial is not designed to test specific biomarker-related statistical hypotheses, the analysis of these data should be viewed as exploratory and hypotheses-generating. Analyses may include how the peripheral T-cell activation and proliferation and cytokine release distribute between the type of responder groups. Descriptive analysis will be performed, and further details for additional analyses will be defined in the SAP. Results from exploratory biomarker assessments may be documented in separate reports.

Biomarkers, including pharmacodynamic markers, may be listed, tabulated, and plotted when deemed appropriate. Analyses may be stratified by clinical covariates or molecular subgroups using the appropriate statistical methods (eg, ANCOVA), proportional hazards regression, or Kaplan-Meier methods) depending on the endpoint and the hypotheses. Baseline biomarker levels or changes in biomarker levels may be assessed for correlation with tumor response and other clinical endpoints to identify responsive or resistant subgroups, as well as biomarkers or pathways attenuated following treatment.

Additional analyses that may be performed after the completion of the end-of-trial CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this trial combined with data from other trials or the analysis of biomarkers

generated from samples collected during the trial but analyzed after the database lock and completion of the CSR. These analyses will be described in an addendum of the SAP, or in a standalone analysis plan document, as appropriate.

Planned analyses are based on the availability of clinically valid assays and may be deferred if emerging trial data show no likelihood of providing useful scientific information.

9.4.7 Immunogenicity Analyses

ADA titers to GEN1053 in monotherapy or in combination therapy will be separately listed and positive/negative host immune response to GEN1053 and presence of neutralizing antibodies may be summarized (positive/negative). The presence of PK concentrations above a certain threshold, which depend on the drug tolerance of the ADA assay at the same time as the ADA sample, may make the ADA undetectable and hence render nonconclusive. The association between positive/non-positive ADA, PK (predose, AUC, C_{max}) and safety findings will be explored.

9.4.8 Health Economics

Not applicable

9.4.9 Multiplicity

There will be no correction for multiple tests.

9.4.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the ORR will be estimated and plotted within each category of the following classification variables (where applicable):

- Age category (eg, <65, ≥65 years)
- Sex (female, male)
- Race category (where permitted)
- ECOG status
- Geographic region of enrolling site
- Histology (eg, squamous, nonsquamous)
- Smoking status
- Prior therapy

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

9.5 Efficacy Monitoring in Expansion Cohorts

The Expansion part will be conducted in at least 2 tumor types using the Bayesian PPoS with a maximum sample size of 40 per indication and treatment (both mono- and combination therapy).

The efficacy in each Expansion cohort will be monitored utilizing the Bayesian efficacy monitoring via predictive probabilities (Lee and Liu, 2008). In particular, the PPoS will be calculated when (at minimum) 2 scans from the first 10 subjects in the Expansion cohort have been locally reviewed. The next futility inspection takes place when data from 20 subjects have been locally reviewed.

At the end of the Expansion cohort, the success criteria are defined as the posterior probability that the confirmed ORR exceeds the ineffective ORR threshold (p_0) with at least 80%. The weights correspond to how likely each outcome is.

If the predicted probability of success is less than 10% the monotherapy Expansion cohort is judged as likely being "futile." However, the threshold of 10% is not considered as a binding futility bar as the Expansion cohort at this stage still is under explorative investigation. The enrollment into the Expansion cohort may also continue (up to maximum 40 subjects) while the scans necessary to derive the response rates in the initial 20 subjects are obtained and reviewed. For the combination therapy Expansion cohort, a 30% threshold determines whether further investigation is judged "futile" or "non-futile." However, again, the criterion is nonbinding.

The ineffective ORR thresholds are tabulated in Table 9-2, with the rates considered to warrant further evaluation of GEN1053 as mono- or combination therapy (p_1). Based on p_0, the number of responders required at the monitoring time to consider the data as a likely "success" (by each case) is presented in Table 9-3.

For calculations, the Bayesian Efficacy Monitoring via Predictive Probability application v1.1.4 at www.trialdesign.org has been utilized, based on the following design parameters:

- Beta(p_0,1-p_0) as prior distribution for the response rate
- No early stopping for efficacy

Table 9-2 The Ineffective ORR Threshold and the Response Rates That Warrant Further Evaluation of the Drug

Cancer Type	**Case A: Mono Therapy** HNSCC	**Case B: Combination Therapy** NSCLC
Ineffective ORR threshold (ORR $\leq p_0$)	p_0=10%	p_0=15%
ORR that warrants further evaluation of the drug	p_1=25%	p_1=30%

HNSCC=head and neck squamous cell carcinoma; NSCLC=non–small cell lung cancer; ORR=objective response rate

Table 9-3 Number of Responders Required at Monitoring Time to Consider Data as a Likely "Success" (by Each Case)

Case	Data Likely Non-futile at 10 Subjects' Monitoring Time	Data Likely Non-futile at 20 Subjects' Monitoring Time	Number of Responses Required to Meet Success Criteria in 40 Subjects	True ORR	Likelihood to Consider Data Futile at any Interim	Likelihood to Meet Success Criteria at Final Analysis
A	N/A	≥2/20	≥6/40	10%	48%	17%
				25%	7%	91%
B	≥2/10	≥4/20	≥9/40	15%	72%	10%
				30%	19%	76%

ORR=objective response rate
Prior distributions: A beta (0.1, 0.9); B beta (0.15, 0.85)

9.6 Data Monitoring Committee

A DMC will be established as noted in Appendix 1.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS – APPENDICES

Appendix 1. Regulatory, Ethical, and Trial Oversight 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.

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.

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, 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 non-compliance, annual written summaries of the trial status, and deviations to the protocol implemented to eliminate immediate hazards to the subjects must be submitted to the IEC/IRB.

Interim reports on the trial and/or 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.

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.

Administrative Procedures

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 monitor or contact information). Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a deviation from the protocol is unavoidable, the investigator or other physician in attendance will contact the sponsor (see the separate sponsor Contact Information page, which 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.

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.

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.

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 (or their legally acceptable representatives [not applicable in EU/EEA]) 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. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal 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 health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations.

By signing the ICF the subject (or legally acceptable representative [not applicable in EU/EEA]) is authorizing such access, including permission to obtain information about survival status, and agrees to allow their trial physician to recontact 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 (or his/her legally acceptable representatives [not applicable in EU/EEA]) 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 (not applicable in EU/EEA) personally dated signature.

Subjects (or his/her legally acceptable representative [not applicable in EU/EEA]) 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 (or legally acceptable representative [not applicable in EU/EEA]) is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject (or legally acceptable representative [not applicable in EU/EEA]) is obtained.

The sponsor will, on an ongoing basis, assess whether reconsent of subjects is needed. A subject who is rescreened is not required to sign another ICF unless the subject's rights, risks regarding trial participation, or well-being has changed since the first ICF was obtained.

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

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 has been pseudonymized to the effect that only authorized individuals can link data to identified individuals.
- A data breach response plan has been established.

The collection and processing of personal data from subjects enrolled in this trial will be limited to those data that are necessary to fulfill the objectives and purposes of the trial and as specifically defined in the protocol.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate

technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place, as detailed above. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or their legally acceptable representative [not applicable in EU/EEA]) 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.

Committees Structure

Dose Escalation Committee:

The DEC will be chaired by the sponsor’s medical monitor (or delegate) and membership will include investigator(s), a sponsor clinical 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.

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

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 prior DLs and treatment doses after the DLT period may also be presented. Recommendations on dose escalation (or de-escalation) will be made by the DEC to the Safety Committee.

Safety Committee:

The sponsor’s SC 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 subjects treated with marketed Genmab drugs. For the GCT1053-01 Dose Escalation phase, the SC will consider the recommendation made by the DEC and make the final decision regarding dose escalation (or de-escalation). Additionally, the SC will consider the DMC's recommendations regarding proceeding of the trial to the next trial design phase including recommendations for the RP2D for both GEN1053 monotherapy and combination therapy. During the Expansion phase, the SC will meet at regular intervals and as needed as per the SC charter.

The SC can 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 SC to evaluate the emerging data. In case of emerging safety issues with potential impact on the trial conduct, the SC will consult the DMC on an ad hoc basis.

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

Data Monitoring Committee:

A DMC will be established to ensure the continuing safety of the subjects enrolled in this trial as an external advisory body. The DMC will assess the totality of safety information of the trial to propose whether the trial can proceed to the subsequent design phase. This committee will consist of at least 3 members with a minimum of 1 medical expert in the relevant therapeutic area; the committee membership responsibilities, authorities, and procedures will be documented in its charter.

During the trial, the DMC will review data with emphasis on safety results at the decision points, when the trial is to proceed to the subsequent trial design phase. The DMC is to recommend whether the risks to trial subjects remain acceptable and that adequate risk mitigation plans are in place to safeguard subjects' safety as the trial progresses. The relevant decision points are:

1. The opening of the combination arm in the Dose Escalation phase 1b

2. The declaration of the RP2D for GEN1053 monotherapy based on the dose escalation in the Monotherapy Dose Escalation phase 1a and the opening of the monotherapy cohort in the Expansion phase

3. The declaration of the RP2D for the GEN1053+IM combination based on the combination therapy dose escalation in the Combination therapy Dose Escalation phase 1b and the opening of the combination cohort in the Expansion phase

The DMC will also be presented with the trial analyses upon trial completion.

All available data, including safety, PK, and pharmacodynamic data, will be reviewed by the DMC. After review, the DMC will make recommendations to the SC regarding the continuation of the trial. The DMC can recommend that the trial should be stopped for unacceptable toxicity based on a risk-benefit assessment. Deaths considered related to GEN1053 will always be assessed by the DMC.

The DMC will also be available on an ad hoc basis, ie, to advise and recommend actions in relation to urgent safety signals, mitigation plans, etc, if requested by the SC. Additionally, if other compounds are to be tested in combination with GEN1053 or/and if alternative doses/schedules are to be tested in the escalation period, the DMC may be consulted for their recommendation. The SC will conclude on any such decision.

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).

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

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 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.

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.

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.

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).

Source Documents and Case Report Form Completion

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
- 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.

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. 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.

Trial and Site Start and Closure

The trial start date will be the first act of recruitment (ie, the first subject 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 GEN1053 and/or IM development. The sponsor may, based on available data, discontinue further development of GEN1053 and/or IM. Following trial termination, the sponsor will make their best effort to provision posttrial access to GEN1053 and/or IM for those ongoing trial subjects with a potential treatment benefit, in accordance with local laws and requirements.

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.

Liabilities and Insurance

The sponsor is responsible for taking out relevant clinical trial insurance in accordance with local law and regulations.

Publication Policy

All information, including but not limited to information regarding GEN1053 monotherapy or GEN1053+IM combination therapy 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 GEN1053 or GEN1053+IM, 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, 2019), the sponsor in conjunction with any collaborative group(s), shall have the right to publish such primary (multicenter) data and information as per the 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), 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.

Appendix 2. Clinical Laboratory Tests

Laboratory tests required by the protocol are specified in Table 10-1 below. The laboratory reports must be filed with the source documents.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.

Local laboratory values must be obtained 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.

For AE reporting of laboratory test abnormalities refer to Appendix 3.

Table 10-1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology (local laboratory)	Hematocrit Hemoglobin mean platelet volume (MPV) Platelet count RBC count	RBC indices: mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC) % reticulocytes	WBC count with differential[1] Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Biochemistry (local laboratory)	Albumin	Blood urea nitrogen (BUN) or urea.	Gamma glutamyl transferase (GGT)	Phosphate
	Alanine aminotransferase (ALT)	Calcium	Glucose	Potassium Sodium
	Alkaline phosphatase	Chloride	Glycosylated hemoglobin	Total and direct bilirubin
	Amylase	C-reactive protein	Lactate dehydrogenase (LDH)	Total protein
	Aspartate aminotransferase (AST)	Creatinine (estimated glomerular filtration rate [GFR] by the MDRD formula)	Lipase Magnesium	Uric acid
Coagulation factors (local laboratory)	Prothrombin time (PT)	International normalized ratio (INR)	Activated partial thromboplastin time (aPTT)	
Urinalysis (local laboratory)	Leukocytes	Protein	Urine pregnancy	
Other tests (local laboratory)	Serum β-hCG[2] Hepatitis B testing: antibodies to hepatitis B surface antigen (anti-HBs), antibodies to hepatitis B core antigens (anti-HBc), hepatitis B surface antigen (HBsAg) Triiodothyronine (T3) and thyroxine (T4), TSH HIV testing is required at screening only if required per local health authorities or institutional standards			

1. WBC differential in either absolutes or percentages.
2. Serum beta-human chorionic gonadotropin (β-hCG) should be collected at Screening only; urine pregnancy tests may be conducted at other visits. A woman of childbearing potential must have a negative serum β-hCG at Screening. Subjects that are postmenopausal or permanently sterilized (see Appendix 4) can be considered as not having reproductive potential.

Appendix 3. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Definition of Adverse Events

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.

Definition of Serious Adverse Events

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 preplanned treatment for a preexisting 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.

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 defined for this protocol in Section 8.4.1.1 and discussed further in the IB.

Definition of 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.

Reporting Period

This is trial specific and defined in Section 8.4.2, Adverse Event Reporting. Events requiring immediate reporting are listed in Section 8.4.3.

Procedures for Recording and Reporting

All AEs, serious or nonserious, must be documented.

- The diagnosis/cause of an AE should be documented rather than the symptoms of the AE.
- If no diagnosis is available, then each sign and symptom should be documented as 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: A CTCAE grade 3 or 4 laboratory abnormality does not automatically indicate an SAE.

Disease-related events and outcomes not qualifying as AEs or SAEs are trial specific and provided in Section 8.4.5.

Evaluation of Adverse Events

Severity

Toxicities will be graded for severity according to the NCI-CTCAE, version 5.0. Exception are CRS events, which are to be graded by ASTCT criteria (Lee et al., 2019).

Relationship to Trial Treatment

The investigator must assess whether or not the event is related to the individual trial treatment. If a subject is on combination treatment, this assessment should be done separately for each trial treatment. 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 IB.

Annual Safety Reporting by Sponsor

Within the EU, the sponsor will submit an Annual Safety Report for GEN1053, including data on multi-drug therapy.

Appendix 4. 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 GEN1053 administration; all men must also refrain from donating sperm during the trial and for 6 months after receiving the last dose of GEN1053. When the IM is selected, the duration since last dose will be defined.

Female subjects of reproductive potential must agree to use adequate contraception during and for 6 months after receiving the last dose of GEN1053. When the IM is selected, the duration since last dose will be defined. Adequate contraception is defined as highly effective methods of contraception (see Table 10-2). 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 GEN1053 or IM.

Table 10-2 Highly Effective Methods of Contraception

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]:
  - Oral
  - Injectable
  - Implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[b, c]
- Sexual abstinence[d]

a. Hormonal contraception may be susceptible to interaction with GEN1053 or IM, 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.

Table adapted from "Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1." (CTFG, 2020).

Appendix 5. 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 NSCLC, HNSCC, and other malignant solid tumors; the dose response and/or prediction of response to GEN1053; 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 .

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. 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 Appendix 1 for subject confidentiality.

Appendix 6. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status	
Score	**Performance Status**
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.

Appendix 7. 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.
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 study.
Progressive disease (PD)	At least one 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 study) 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‡

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 preexisting lesions).

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

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

Appendix 8. Statistical Methodologies – BLRM and mBOIN

BLRM

A 2-parameter BLRM guided by the EWOC principle will be used to make dose recommendations and estimate the MTD during the escalation phase of the trial. The DLT target interval is taken to be (0.16, 0.33).

For each available DL, including intermediate doses (d=1,…,$n_{max\ DL}$), the log odds of the DLT rate (πd) is modeled as a linear function of logarithmic standardized dose d (computed by dividing by the reference dose d^*):

$$log(\pi_d/(1-\pi_d)) = \alpha_0 + \alpha_1 log(d/d^*)$$

For this trial a bivariate normal prior is placed on (α_0, log(α_1)), with α_0 marginally N(m_1, s_1), log(α_1) marginally N(m_2, s_2), and a correlation of r. The prior was selected to be minimal informative in the sense of Neuenschwander et al (2008). In order to determine a reasonable prior distribution, let us make assumptions that seem reasonable:

1. Any toxicity probability above 0.1 would be very unlikely at the minimum dose
2. Any toxicity probability below 0.2 would be very unlikely at the maximum dose

So, assuming the prior probability of DLT rate exceeds 0.1 at the lowest dose is at most 5%, and, that the probability of the rate falls below 0.2 at the highest dose is at most 5%, a minimal informative prior distribution is derived as starting point for the calculations. Further, the prior medians of π_d for all DLs are assumed to fall on a straight line in log dose on logit scale. These conditions determine the parameters of a minimal informative prior beta distribution specific for each DL. A final step identifies a bivariate normal distribution that minimizes the distance between quantiles (0.05, 0.5, 0.95) of the beta distributions.

EWOC: a DL is considered to be safe to escalate to if there is less than 25% probability that the DLT rate on the corresponding DL during the DLT evaluation period is 33% or more. At any time during the trial, the method will not assign a subject to a dose that is not safe by this definition. If all DLs are considered unsafe, the trial will stop early, with the MTD estimated to be below the experimental dose range.

The scenarios outlined in below Table 10-3 were evaluated by simulations using the R package crmPack (Sabanés Bové et al., 2019). The results are summarized in Table 10-4.

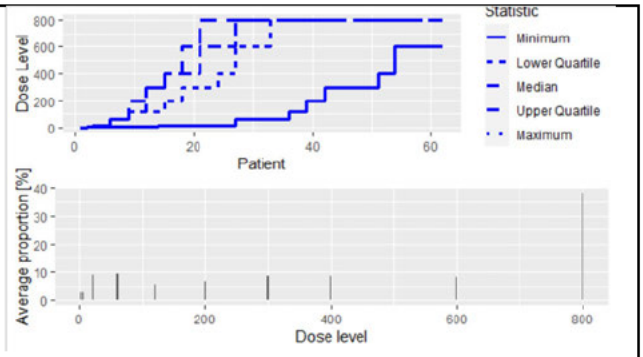
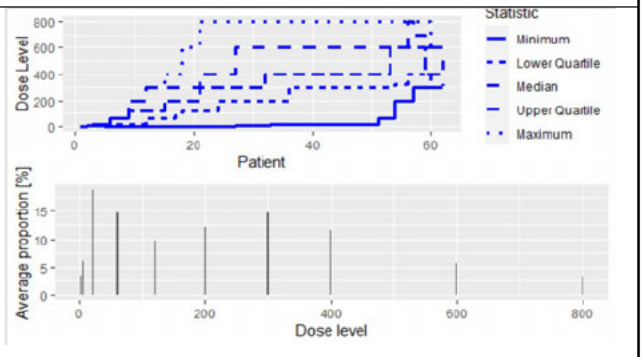
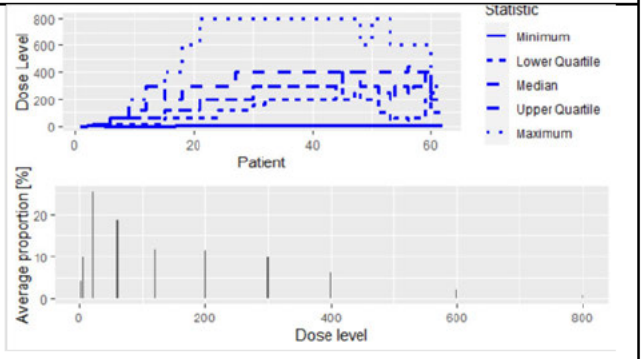
Table 10-3 Six Scenarios Defined Through the DLT Probabilities on Ten DLs (Including Three Intermediate DLs).

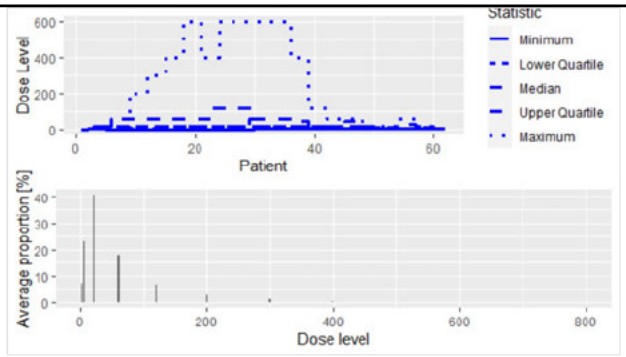
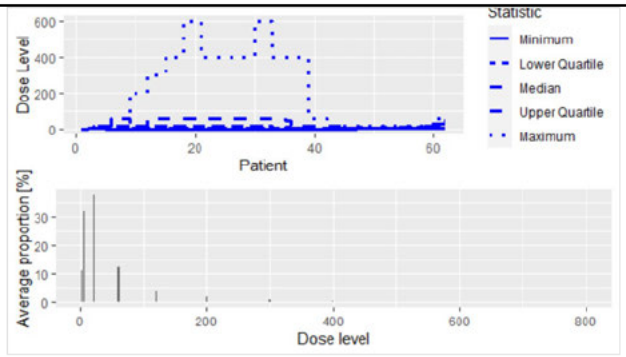
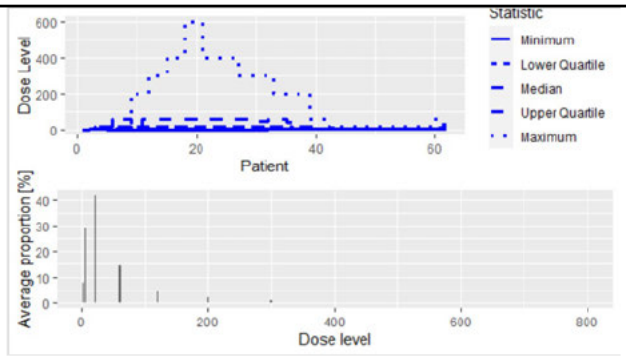
Scenario	DL1 CCI	DL2 CCI	DL3 CCI	DL4 CCI	DL5 CCI	DL6 CCI	DL7 CCI	DL8 CCI	DL9 CCI	DL10 CCI
1	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	**0.1**
2	0.05	0.06	0.07	0.08	0.09	0.1	0.2	**0.25**	0.3	0.35
3	0.07	0.08	0.1	0.13	0.14	0.18	**0.25**	0.3	0.4	0.5
4	0.09	0.15	0.2	**0.25**	0.35	0.4	0.45	0.5	0.55	0.6
5	0.15	0.2	**0.25**	0.3	0.35	0.4	0.45	0.5	0.6	0.7
6	0.1	0.15	**0.25**	0.35	0.45	0.55	0.65	0.7	0.8	0.9

DL=dose level; DLT=dose-limiting toxicity.

Scenarios in terms assumed true DLT rates.

Table 10-4 Operating Characteristics of BLRM Based on 6 Scenarios and 1,000 Simulations

Scenario 1. Number of subjects overall: mean 47 (29, 62)	
Scenario 2. Number of subjects overall : mean 32 (23, 44)	
Scenario 3. Number of subjects overall : mean 29 (17, 41)	

Scenario 4. Number of subjects overall: mean 22 (14, 31)	
Scenario 5. Number of subjects overall: mean 20 (13, 29)	
Scenario 6. Number of subjects overall: mean 21 (14, 31)	

mBOIN

An mBOIN design will be utilized to make optimal recommendations at end of each observed cohort. The target DLT rate is set to $\phi = 30\%$ with the assumptions that $\phi_1 = 0.6\phi$ is the highest sub-therapeutic DLT rate and $\phi_2 = 1.4\phi$ is the lowest DLT rate that has excessive toxicity. Set overdose control equal to 0.95. Under these assumptions, the thresholds that minimize the decision error at end of each cohort are $\lambda_1 = 24\%$ and $\lambda_2 = 36\%$.

Operating characteristics for the BOIN method are displayed in Table 10-5.

Table 10-5 Operating Characteristics of BOIN Based on 6 Scenarios and 10,000 Simulations

Simulation Scenario		DL1	DL2	DL3	Total Mean	%Early Stopping
1	Prob(DLT)	1%	2%	3%	-	-
	Selection(%)	0%	0.1%	99.9%	-	0%
	% Pts treated	9.7%	10.6%	79.7%	11.3	-
2	Prob(DLT)	3%	4.5%	10%	-	-
	Selection (%)	0.1%	0.1%	99.8%	-	0%
	% Pts treated	10.8%	13.9%	75.3%	12	-
3	Prob(DLT)	17%	20%	30%	-	-
	Selection (%)	11.8%	26.1%	60.2%	-	1.9%
	% Pts treated	22.4%	33.3%	44.3%	15.6	
4	Prob(DLT)	20%	30%	40%	-	-
	Selection (%)	27.4%	40.6%%	28.8%	-	3.2%
	% Pts treated	31.9%	39.2%	29%	16.9	
5	Prob(DLT)	30%	40%	50%	-	-
	Selection (%)	52.9%	25.3%	9.6%	-	12.2%
	% Pts treated	47.3%	34.8%	17.9%	14.7	-
6	Prob(DLT)	40%	50%	60%	-	-
	Selection (%)	53.6%	12.2%	1.7%	-	32.5%
	% Pts treated	60.7%	28.5%	10.8%	12	-

BOIN=Bayesian optimal interval; DLT=dose-limiting toxicity; N_{95}=95% quantile of number subjects dosed across 10,000 simulations; Prob=probability; Pts=patients.

Based on output from BOIN application provided by https://trialdesign.org/

Appendix 9. Country-Specific Considerations

Authorization status in EU for IMP(s) and AMP(s) is summarized in Table 10-6.

Table 10-6 IMP/AMP EU Authorization Status

Drug Name	IMP or AMP	EU Authorization Status
GEN1053	IMP	Unauthorized
IM	TBD	TBD

AMP=auxiliary medicinal product; EU=European Union; IM= immunomodulator; IMP=investigational medicinal product; TBD=to be decided.

France specific requirements are summarized in Table 10-7.

Table 10-7 France-Specific Requirements

Section	Country-specific language
5.2, Exclusion Criterion #7FR	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.

Appendix 10. Abbreviations and Definitions

Abbreviation	***Definition***
1L	first line
2L	second line. If followed by "+": second line or higher.
5-FU	fluorouracil
ADA	antidrug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AMP	auxiliary medicinal product
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
anti-HBc	antibody to the hepatitis B core antigen
anti-HBs	antibody to the hepatitis B surface antigen
APC	antigen-presenting cell
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration-time curve
β-hCG	beta-human chorionic gonadotropin
BAL	bronchoalveolar lavage
Baseline	Baseline is the last available measurement prior to first dosing of trial treatment, if not otherwise specified.
BLRM	Bayesian logistic regression model
BOIN	Bayesian optimal interval method
BOR	best overall response
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRCA	breast cancer
%CV	percent coefficient of variation
C	cycle
CBC	complete blood count
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
cfDNA	cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations
C_{max}	maximum (peak) concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPI	checkpoint inhibitor
CPS	combined positive score
CR	complete response
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	clinical trials facilitation group
C_{trough}	predose trough concentration
CTLA-4	cytotoxic T-lymphocyte-associated-protein 4
ctDNA	circulating tumor-derived deoxyribonucleic acid

Abbreviation	***Definition***
CXCL9/10	CXC motif chemokine ligand 9/10
D/d	day(s)
DC	dendritic cell
DCR	disease control rate
DDS	dose determining set
DEC	dose escalation committee
DL	dose level
DLT	dose-limiting toxicity
DMC	data monitoring committee
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DoR	duration of response
DRF	dose range finding
EC	effective concentration
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EEA	European Economic Area
EGFR	epidermal growth factor receptor
ER	estrogen receptor
EU	European Union
EWOC	escalation with overdose control
FAS	full analysis set
Fc	fragment, crystallizable
FcγR	Fc gamma receptor
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxyglucose-positron emission tomography
FIH	first-in-human
FSH	follicle-stimulating hormone
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
GM-CSF	granulocyte/macrophage colony-stimulating factor
GzmB	granzyme B
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest nonseverely toxic dose
HPV	human papillomavirus
hr	hour(s)
IAS	immunogenicity analysis set
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	immune confirmed progressive disease
iCR	immune complete response

Abbreviation	*Definition*
iDCR	immune disease control rate
iDoR	immune duration of response
IEC	independent ethics committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
IM	immunomodulator
IMP	investigational medicinal product
INR	international normalized ratio
iORR	immune overall response rate
iPFS	immune progression-free survival
iPR	immune partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
IRT	interactive response technology
iSD	immune stable disease
iUPD	immune unconfirmed progressive disease
IV	intravenous(ly)
KRAS	KRAS proto-oncogene, GTPase
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LLOQ/2	half the lower limit of quantification
MET	MET proto-oncogene, receptor tyrosine kinase
mAb	monoclonal antibody
CCI	CCI
MAD	maximum administered dose
mBOIN	modified Bayesian Optimal Interval
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MHC	major histocompatibility complex
MoA	mechanism of action
mOS	median overall survival
MPV	mean platelet volume
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
NCI	National Cancer Institute
NGS	next-generation sequencing
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non–small cell lung cancer
NTRK1/2/3	neurotrophic receptor tyrosine kinase 1/2/3
ORR	objective response rate
OS	overall survival
PAD	pharmacologically active dose
PAS	pharmacokinetic analysis set
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic

Abbreviation	*Definition*
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic(s)
PLT	platelet
PPoS	predictive probability of success approach
PR	partial response
PRO	patient-reported outcome(s)
PT	prothrombin time
RET	ret proto-oncogene
Q3W	every 3 weeks
QA	quality assurance
QW	weekly
QTc	corrected QT interval
QTcF	QT intervals using Fridericia's correction
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
RP2D	recommended phase 2a dose
RT	radio therapy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	safety committee
sCD27	soluble CD27
SCr	serum creatinine
SD	stable disease
SJS	Stevens-Johnson syndrome
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
T4	free thyroxine
T3	total triiodothyronine
T1DM	type 1 diabetes mellitus
TCGA	the Cancer Genome Atlas Program
TCR	T-cell antigen receptor
TEAE	treatment-emergent adverse event
TEN	toxic epidermal necrolysis
TRAE	treatment-related adverse event
TME	tumor microenvironment
t_{max}	time to maximum (peak) concentration
TNF	tumor necrosis factor
TNM	tumor nodes metastasis
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UNS	unscheduled
US	United States
WBC	white blood cell

11 LAY PROTOCOL SYNOPSIS

Protocol Title	First-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate the safety of GEN1053 as monotherapy and in combination with an immunomodulator in subjects with malignant solid tumors	
Brief Title	A study to evaluate safety, tolerability, and preliminary effect of the GEN1053 antibody on malignant solid tumors as monotherapy and in combination.	
Protocol Number	GCT1053-01	
Regulatory Agency Identifier Number(s)	**EU CT No.**	2022-502419-12-00
	NCT No.	NCT05435339
Rationale	GEN1053 is an antibody that binds to a molecule on cells involved in killing cancer cells. Studies in cells and animals have indicated that GEN1053 can stimulate the fighting of cancer by binding to these cells. GEN1053 may not only work alone but also together with other cancer drugs. The purpose of the first part of this trial is to identify doses of GEN1053 that can either work alone or together with other cancer drugs in fighting cancer and determine the severity of possible side effects. The purpose of the second part of this trial is to determine the severity of the possible side effects and the potential benefit of GEN1053 or potential added benefits of combining GEN1053 with other cancer drugs in patients with various cancers in the head and neck or lung.	
Objectives/Endpoints	***Primary Objective(s)***	***Primary Endpoint(s)***
	• Determine the optimal dose or highest tolerable dose of GEN1053 when given alone or when given together with other cancer drugs • Measure and assess the types and frequencies of side effects and tolerability of GEN1053 when given alone or in combination with other cancer drugs	• How often side effects occur and how serious they are • How often laboratory values are outside the normal range and by how much
	Secondary Objective(s)	***Secondary Endpoints(s)***
	• Evaluate how the body handles GEN1053	• Concentration levels of GEN1053 in the blood and how they change over time
	• Evaluate if the body reacts to GEN1053	• Concentration levels of compounds in blood called an “anti-drug antibody” that the body may produce to counteract GEN1053
	• Evaluate how the tumor is affected by GEN1053 or GEN1053 in combination with other cancer drugs	• Measures of how the tumor has reacted (shrinkage or growth) to treatment
Brief Summary	Participants will receive either GEN1053 alone or in combination with other cancer drugs into the vein once every 3 weeks. All participants will receive active drug; no one will receive placebo.	

	All participants will receive study treatment for an estimated period of 6 months, or until: • the cancer progresses • there are side effects requiring that treatment be stopped • the patient decides to withdraw • the doctor believes it is in the patient's best interest to stop treatment. Participation in the study 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, computerized X-rays) to monitor whether the treatment is safe and effective. The study duration (including screening, treatment, and follow-up) for each participant is estimated to be about 20 months.
Trial Population	In the first part: Patients with various incurable cancers, 18 years of age or older, with acceptable kidney and liver function. In the second part: Patients with cancers in the head and neck or certain types of lung cancer, 18 years of age or older, with acceptable kidney and liver function.
Ethical Considerations	Research in cells and animals suggests that GEN1053 may be effective in treating cancer in humans and may also work together with other cancer drugs. Being treated with GEN1053 alone or in combination with other cancer drugs in this trial may or may not make the health better for an individual patient. Although the health of one patient may not get better, other patients may benefit from the knowledge gained from this trial in the future. Patients' health will be observed and monitored during the trial and all tests and procedures performed throughout the trial are done to ensure that GEN1053 or GEN1053 in combination with other cancer drugs is both safe and effective (that is, the drugs can fight cancer). Overall, the possible benefits of this trial outweigh the risks.

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Protocol Amendment Summary of Changes

Protocol Amendment 1_EU-1 (07 May 2024)

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

Overall Rationale for the Amendment:

This amendment was prepared to comply with the European regulation 536/2014 content and format requirements and to update with information from clinical experience in the trial.

Summary Description of Changes:

Section	Description of Change	Brief Rationale
Global	Administrative and editorial corrections (including typographical, formatting, and grammatical) have been made throughout the protocol.	
Title Page	Format update and administrative information added.	To provide more administrative information.
Sponsor Information Page	Additional countries and sponsor address updated.	To reflect updated information.
Investigator Agreement	Page added.	To reflect the investigator agreement page.
Section 1.1	Aligned with updates in the remainder of the document and added a row for the indication.	To reflect changes in the remainder of the protocol.
Section 1.3	Clarified that follow-up windows relate to trial treatment and that for the monotherapy dose escalation part, the last subject discontinuing treatment will not go into survival follow-up. It is further specified that immunophenotyping is in whole blood.	To clarify.
Section 2.2.2.1	HLA-DR removed from the list of expression marker of activation.	Due to updated results.

Section	Description of Change	Brief Rationale
Section 2.3.2.1	Summary of potential risks added.	To reflect current clinical experience.
Section 2.3.3	Overall B/R statement updated	To reflect updated information.
Section 3	Clarified that PK assessments only apply for GEN1053.	To clarify.
Section 4.1	Statement on patient input to trial design added.	To clarify.
Section 4.3.1	Header for IMP added.	
Section 4.3.2	Section added for AMP dose and schedule rationale.	To clarify.
Section 4.4	Sections added to clarify primary completion date, estimated trial duration, and end of trial definition.	To clarify.
Section 5.1	Clarified that a legally acceptable representative does not apply within EU/EEA.	To clarify.
Section 5.2	Exclusion criteria relating to prior PD-1/PD-L1 treatment added.	Based on potential risk updates.
Section 5.3	Details on screening failure information added.	To clarify.
Section 6.1	IMP and AMP information added. In addition, trial treatment terminology has been applied throughout the document.	To clarify.
Section 6.2 (previously Section 6.1.4)	Clarified that this related to product complaint handling and subsections merged into main section.	To clarify.
Section 6.3.2	Updated to reflect trial treatment and clarifying option to make drug accountability at site closure.	To clarify.
(Previous) Section 6.5.4	Rescue medication section removed.	Rescue medication not applicable.
Section 6.6.3	Conditions for concomitant therapy documentation beyond the safety follow-up period clarified.	To clarify.
Section 6.7.1	Re-emphasized that DLT are only to be considered DLTs if occurring within the DLT evaluation period	To clarify.
Section 6.7.2.3	Specific AEs treatment context clarified.	To clarify.
Section 6.8	Overdose information compiled here.	To compile overdose information within the trial treatment section.

Section	Description of Change	Brief Rationale
Section 6.9.1	Further details added on continued access to trial treatment and end of trial.	To clarify.
Section 7.1	Discontinuation details updated.	To clarify.
Section 7.1.2	Details on survival status follow-up clarified.	To clarify.
Section 7.2	Information on reason for withdrawal documentation and ability to request destruction of samples added.	To clarify.
Section 7.3	Procedures for lost to follow up updated.	To clarify.
Section 8	Assessment timing statement added.	To clarify.
Section 8.3.1	Conditions for physical examination reporting as AEs clarified.	To clarify.
Section 8.4.1.1	Clarified that AESIs are irrespective of relatedness to trial treatment.	To clarify.
Section 8.4.2	Table added on AE reporting period and requirements, reference to Section 1.3 removed and reference to Section 6.2 added.	To clarify.
Section 8.4.3	Process for immediate reporting clarified.	To clarify.
Section 8.4.3.1	Section on second primary malignancies added.	To clarify.
Section 8.4.3.2	Specified that it is SAE and removed the bullet point now covered by Section 8.4.3.1.	To clarify.
Section 8.4.3.3	Simplified, giving reference to Section 6.8 for overdose. Medication error for concomitant medication clarified.	To clarify.
Section 8.4.3.4	Reporting process details for pregnancies clarified.	To clarify.
Section 8.4.3.5	Specified that reporting for AESIs is 24 hours from awareness.	To clarify.
Section 8.4.4.1	Section on AMP reporting requirements added.	To clarify.
Section 8.4.5	The use of progression terminology updated, and redundant reporting statement removed.	To clarify.
Section 8.4.6	Redundant information covered in Section 8.4.3.1 removed.	To clarify.
Section 8.4.7	Updated to refer to the IB for warnings and precautions.	To clarify.

Section	Description of Change	Brief Rationale
Previous Section 8.5	Section removed as now compiled in Section 6.8.	To compile overdose information within the trial treatment section.
Section 8.5	Specified that PK assessment only applies for GEN1053.	To clarify.
Section 8.7	Section restructuring and removal of redundant information in the previous Section 8.8.1.9 after merging with the previous section 8.8.1.8.	For a more logical section structure.
Section 8.8	Clarified that the ADA assessments only relate to GEN1053.	To clarify.
Section 9	Interim and primary analysis designations clarified.	To clarify.
Section 9.2	Reference to efficacy monitoring in Section 9.5 added.	To clarify.
Sections 9.3.5 and 9.3.6	Clarified the PK and immunogenicity is only for GEN1053; either as mono therapy or combination therapy.	To clarify.
Section 9.4	Baseline definition statement added.	To clarify.
Section 9.4.4	Clarified that PK is only for GEN1053 and reference to compartmental modeling removed.	To clarify.
Section 9.4.7	Clarified that ADA is only for GEN1053.	To clarify.
Section 9.4.10	Clarified that the analyses relate to ORR.	To clarify.
Appendix 1	• Reference to 21 CFR and European regulation 536/2014 for clinical trials added. • Clarified that the legally acceptable representative is not applicable in EU/EEA. • IRB/IEC potential access to subjects' identification register for long-term follow up added. • Information on potential data breach added. • Reference to EudraCT removed. • Option for remote monitoring added. • Added that limited and redacted source documents can be shared with sponsor for screening eligibility, where permitted by local regulations. • eCRF and source data details added. • eCRF correction details updated.	To clarify.

Section	Description of Change	Brief Rationale
	• Start date definition updated. • CSR description removed.	
Appendix 2	• Specified that it can be blood urea nitrogen or urea assessment.	To clarify.
Appendix 3	• Bullet list structure for SAE definition revised (no content change). • Details on annual safety reporting within the EU added. • Reference to Section 8.4.6 for AE and SAE follow-up removed.	For readability and to clarify.
Appendix 4	Male reproductive potential and contraception details added together with a note that details relating to the IM will be added when defined for both sexes.	To clarify.
Appendix 5 (New)	Appendix added on sample storage and destruction.	To clarify.
Appendix 9	IMP and AMP EU authorization status added.	To clarify.
Appendix 10	Abbreviations and Definitions updated.	To clarify.
Section 11	Lay protocol synopsis added.	As required by the European regulation 536/2014.