

CLINICAL TRIAL PROTOCOL

A Phase 1 Dose Finding and Phase 2 Randomized, Open-Label Trial to Evaluate the Safety and Clinical Activity of Immunoradiotherapy Combinations as a Treatment Option for Subjects With Metastatic Solid Tumors

Protocol Number:	GCT1042-02
Brief Title:	A Safety and Antitumor Activity Trial of Immunoradiotherapy Combinations as a Treatment Option for Subjects with Metastatic Solid Tumors
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** This protocol was approved via electronic signature on the approval page appended to the document.

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SPONSOR INFORMATION PAGE

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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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Abbreviations

Abbreviation	Definition
β-hCG	beta-human chorionic gonadotropin
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
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
CCI	
BOR	best overall response
BRAF	v-Raf murine sarcoma viral oncogene homolog B
BRCA	breast cancer susceptibility
C1D1	cycle 1 day 1
CA19-9	carbohydrate antigen 19-9
CD	cluster of differentiation
CEA	carcinoembryonic antigen
CCI	
CI	confidence interval
C _{max}	maximum (peak) concentration
CNS	central nervous system
CPI	checkpoint inhibitor
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor-derived deoxyribonucleic acid
CTIS	Clinical Trials Information System
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
DC	dendritic cell
DCR	disease control rate
DD1	Dose Day 1
DEC	dose escalation committee
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EU	European Union
FAS	full analysis set
Fc	fragment crystallizable
FcγR	Fc-gamma receptor

Abbreviation	Definition
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
GDPR	General Data Protection Regulation
GEJ	esophagogastric junction
GFR	glomerular filtration rate
GM-CSF	granulocyte/macrophage colony stimulating factor
GTV	gross tumor volume
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	receptor tyrosine-protein kinase erbB-2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
HNSCC	squamous cell carcinoma of the head and neck
HPV	human papillomavirus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
iCPD	immune confirmed disease progression (according to iRECIST)
iCR	immune confirmed complete response (according to iRECIST)
IEC	independent ethics committee
IFN- γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	investigational medicinal product
INR	international normalized ratio
iPR	immune confirmed partial response (according to iRECIST)
CCI	
IR	high-dose ionizing radiation
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 confirmed stable disease (according to iRECIST)
ISH	in situ hybridization
ITV	internal target volume
IV	intravenous(ly)
KRAS	Kirsten rat sarcoma virus
LCMV	lymphocytic choriomeningitis virus
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAD	maximum administered dose
MAS	macrophage activation syndrome
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MLR	mixed lymphocyte reaction

Abbreviation	Definition
MMR	mismatch repair
MoA	mechanism of action
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
NCI	National Cancer Institute
CCI	
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
OMD	oligometastatic disease
ORR	objective response rate
OS	overall survival
PALB2	partner and localizer of BRCA2
PD	progressive disease
PDAC	pancreatic ductal adenocarcinoma
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PI	package insert
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome(s)
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thrombin time
PTV	planning target volume
Q3W	every 3 weeks
RB1	retinoblastoma 1
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
RT	radiotherapy
SAA	serum amyloid A
SABR	stereotactic ablative radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBRT	stereotactic body radiotherapy
SC	safety committee
SCLC	small cell lung cancer
SCr	serum creatinine
SD	stable disease
SOC	standard of care
SOP	standard operating procedure
SPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reaction
T3	total triiodothyronine
T4	free thyroxine
TAA	tumor-associated antigen
CCI	
TCR	T-cell receptor
CCI	
TNBC	triple-negative breast cancer

<i>Abbreviation</i>	<i>Definition</i>
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
WOCBP	women of child-bearing potential

Protocol Amendment Summary of Changes

Protocol Amendment 4 (25 Jul 2024)

This amendment is considered to be a nonsubstantial 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:

The protocol is being amended to ensure compliance with EU Clinical Trial Regulation 536/2014.

The amendment changes are summarized below. As applicable, changes included in the summary of changes table are also incorporated in the Trial Synopsis. Section numbers and titles are as per Amendment 4.

Description of Changes:

Section	Description of Change	Brief Rationale
2.4 Benefit Risk Assessment; 4.3 Dose and Schedule Rationale; 6.1 Trial Treatment(s) and Therapy Administered; 10 Supporting Documentation and Operational Considerations	Provide required information for drugs classified as IMPs Add new subsections	EU CTR compliance
2.4.2.1 GEN1042	Update the potential risk of “neutropenia” to “neutrophil count decreased”	Most of the event terms reported in the GEN1042 program were updated from neutropenia to neutrophil count decreased
4.1.3 Patient Input Into Design	Add new subsection	EU CTR compliance
4.4.1 Estimated Trial Duration for an Individual Subject; 4.4.2 End of Trial and Estimated Trial Duration	Add new subsection	EU CTR compliance
6.7.1 Subject Contact and Trial Treatment After the End of the Trial	Add text about continued treatment after end of trial	Alignment with current Genmab protocol template
8.4.3.2 Drug-Induced Liver Injury	Editorial change	For clarification and consistency (as defined by Hy’s law)
10 Supporting Documentation and Operational Considerations	Add subsection headings	Alignment with current Genmab protocol template
10.1.6 Informed Consent Process	Remove “legally acceptable representative” throughout section	EU CTR compliance

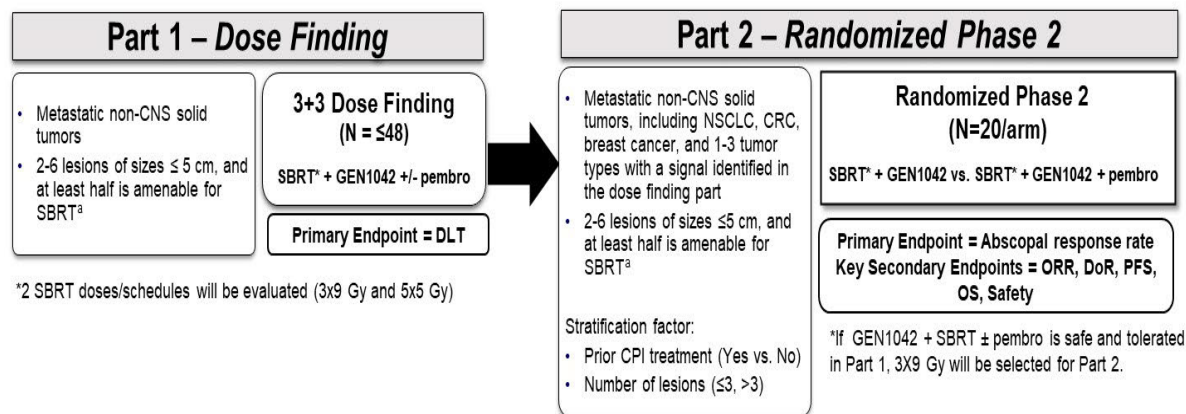
Section	Description of Change	Brief Rationale
10.1.7 Data Protection	Add additional paragraphs to address what is done in case of a potential data breach	EU CTR compliance
10.1.9 Dissemination of Clinical Trial Data	Add additional paragraph to state intention to register trial and publicly disclose results according to local regulations	EU CTR compliance
10.2.4 Annual Safety Reporting by Sponsor	Add new subsection	EU CTR compliance
10.4 Sample Storage and Destruction	Add new subsection	EU CTR compliance
11 Lay Protocol Synopsis	Add new section	EU CTR compliance

CTR=Clinical Trial Regulation; EU=European Union; IMP=investigational medicinal product.

1 PROTOCOL SUMMARY

1.1 Schema

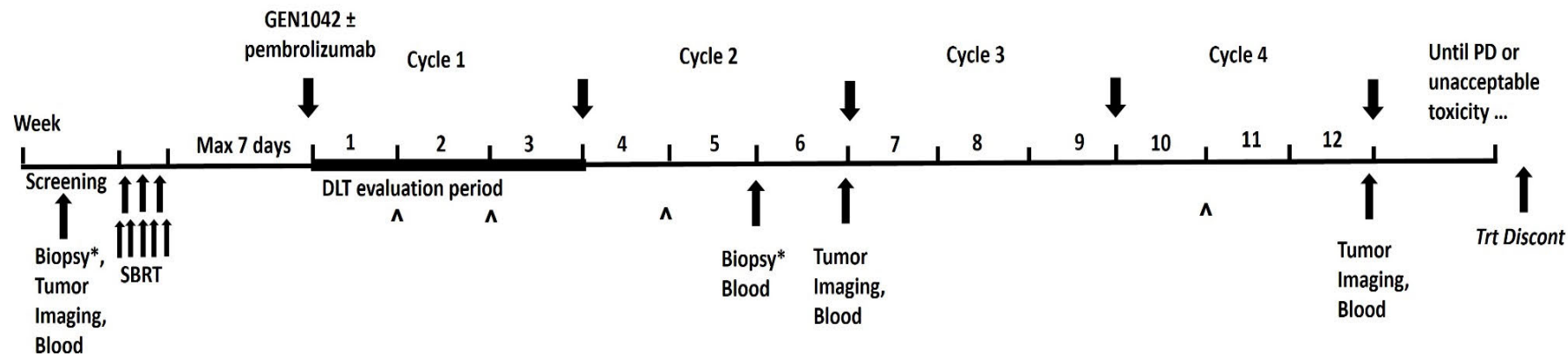
Figure 1-1 Schematic Overview of the Trial – Part 1 and Part 2



Abbreviations: CNS=central nervous system; CPI=checkpoint inhibitor; CRC=colorectal cancer; DLT=dose-limiting toxicity; DoR=duration of response; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; pembro=pembrolizumab; SBRT= stereotactic body radiotherapy.

a. One lesion up to 10 cm in diameter is allowed if this lesion can be irradiated (all other lesions must have a size of ≤ 5 cm).

Figure 1-2 Treatment Schema



GEN1042 ± pembrolizumab infusion must commence within 7 days after the last fraction of SBRT, else will be considered a screen failure.
Abbreviations: C=cycle; D=day; DLT=dose-limiting toxicity; IV=intravenous; Max=maximum; PD=progressive disease; SBRT=stereotactic body radiotherapy; TDLN=tumor draining lymph node; Trt Discont=treatment discontinuation.

^Denotes additional intra-dose blood collections. Note: Blood collections will be made pre-IV dose on day 1 of each cycle and days 8 and 15 of Cycles 1 and 2.

*Denotes biopsy (and TDLN when feasible) collections of 1 (planned) irradiated lesion + 1 (planned) out-of-the-field lesion = 2 biopsies:

- At screening
- On-treatment biopsy must be done between C2D15 and prior to C3D1. The biopsy should be collected after imaging.
- At treatment discontinuation and unscheduled if feasible.

1.2 Schedule of Activities

[Table 1-1](#) and [Table 1-2](#) list all assessments for both the dose finding and randomized phase 2 parts of the trial, and assessments performed at each visit are indicated with an “X”.

Dose Finding/Randomized Phase 2:

- [Table 1-1](#) Schedule of Activities – Dose Finding/Randomized Phase 2
- [Table 1-2](#) Schedule for PK, Cytokines, Immunophenotyping, and Immunogenicity (ADA) Samples – Dose Finding/Randomized Phase 2

In addition to the fixed visits during both parts of the trial, it may be necessary to perform some of the assessments at unscheduled time points if deemed clinically necessary by the investigator.

Table 1-1 Schedule of Activities – Dose Finding/Randomized Phase 2

	Cycle/ Visit	Screening	RT Phase (SBRT) ^d	Rd	Cycle 1			Cycle 2		≥ C3	EOT visit	UNS	Post-Tx. Follow-up Visit ^a	Post-Tx. Follow- up Visit ^b	Survival Status Contact ^c
	Cycle Day	D -28 to D - 1	Over 1 week prior to C1D1		D1 ^d	D8	D15	D1	D15	D1			30d after last dose	90d after last dose	Q12W
	Visit Window		+3d			±1d	±3d	±3d	±3d	±3d			+7d	±7d	±14d
Trial Procedure	Protocol Section														
Informed consent ^e		X													
Demographics	8.1.1	X													
Medical history ^f	8.1.3	X													
Inclusion/ exclusion criteria	5.1, 5.2	X			X										
ECOG PS	8.3.5	X ^g			X			X		X	X	X	X		
Prior anticancer therapies	6.5.1	X			X										
Randomization (part 2 only)				X											
SBRT			X ^h												
	Trial Drug														
Dispense/ administer GEN1042 ^d					X			X		X					
Dispense/ administer pembrolizumab ^d					X			X		X					
	Efficacy Assessments														
Imaging/disease assessments		X ^p (prior to SBRT)			Refer to Section 8.2 for details on imaging assessments ⁱ										
	Safety Assessments														
Full physical exam	8.3.1	X													
Brief (symptom-based) physical exam						X	X	X	X	X	X	X			
AEs ^{f,j}	8.4	X	X		X	X	X	X	X	X	X	X	X	X	
Height	8.3.2.1	X													
Body weight	8.3.2.2	X			X			X		X	X	X	X		
Vital signs	8.3.3	X			X			X		X	X	X	X		
Local 12-lead ECG	8.3.4	X													

	Cycle/ Visit	Screening	RT Phase (SBRT) ^d	Rd	Cycle 1			Cycle 2		≥ C3	EOT visit	UNS	Post-Tx. Follow-up Visit ^a	Post-Tx. Follow-up Visit ^b	Survival Status Contact ^c
	Cycle Day	D -28 to D - 1	Over 1 week prior to C1D1		D1 ^d	D8	D15	D1	D15	D1			30d after last dose	90d after last dose	Q12W
	Visit Window		+3d		±1d	±3d	±3d	±3d	±3d	±3d			+7d	±7d	±14d
Trial Procedure	Protocol Section														
	Local Laboratory Tests														
HCV, HBV	8.3.6	X ^l													
Hematology	8.3.6	X ^l			X ^k	X	X	X	X	X	X	X	X	X ^b	
Biochemistry	8.3.6	X ^l			X ^k	X	X	X	X	X	X	X	X	X ^b	
Coagulation factors	8.3.6	X ^m													
Thyroid function tests ⁿ	8.3.6	X ⁿ			X ⁿ					X ⁿ	X	X	X	X ^b	
Urinalysis (when indicated)	8.3.6	X													
Pregnancy test (WOCBP only) ^o	8.3.6	X			X			X		X	X	X	X		
PSA for prostate cancer	8.3.6	X								X ^q					
	Pharmacokinetic														
PK sample Collection	8.6				See Table 1-2										
ADA	8.8				See Table 1-2										
	Central Laboratory Tests														
Pharmacodynamic/biomarkers	8.7				See Table 1-2										
	Ongoing Review														
Concomitant medication	6.5.2				X	X	X	X	X	X	X	X	X	X	
New anticancer therapy													X	X	X
Survival status	8.2.5														X

Abbreviations: ADA=anti-drug antibody; AE=adverse event; β-hCG=beta human chorionic gonadotropin; C=cycle; CT=computed tomography; D/d=day(s); ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOT=end-of-treatment; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; PD=progressive disease; PK=pharmacokinetic(s); PSA=prostate-specific antigen; Q=every; Rd=randomization; RT=radiotherapy; Q12W=every 12 weeks; SAE=serious adverse event; SBRT=stereotactic body radiotherapy; SOC=standard of care; T3=total triiodothyronine; T4=free thyroxine; TSH=thyroid-stimulating hormone; Tx=treatment; UNS=unscheduled; WOCBP=women of child-bearing potential.

a. Subjects discontinuing from treatment for any reason should have a post-treatment safety follow-up visit 30 days (+7 days) after the last dose of trial drug (see Table 8-2). If the subject initiates new anticancer therapy within 30 days of the last dose of trial drug, the safety follow-up visit should be performed prior to starting new anticancer therapy. Once new anticancer treatment is initiated, the subject should move into survival status follow-up.

- b. The safety laboratory assessment is required at treatment discontinuation and the post-treatment follow-up visit 1; it should be repeated at the post-treatment follow-up visit 2 only if trial drug-related toxicity persists.
- c. Survival follow-up contact may be performed as a telephone call, email, or on-site visit. Survival status will be assessed every 12 weeks (± 14 days) from the first dose for up to 2 years, or until the subject's death, whichever occurs first.
- d. SBRT must be completed within a maximum of 10 days. GEN1042 $\pm$ pembrolizumab infusion must commence within 7 days after the last fraction of SBRT. Up to 35 administrations (approximately 2 years) of pembrolizumab (for subjects in the combination therapy cohorts only) may be given. GEN1042 may be continued if pembrolizumab is discontinued.
- e. Informed consent must be obtained before performing any trial-related procedures or assessment and can be collected up to 42 days before C1D1.
- f. Any medical condition (signs, symptoms, and diagnosis) occurring prior to the first dose of SBRT should be documented as medical history. Medical conditions that occur after the ICF is signed and prior to the first infusion should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (eg, SBRT, tumor biopsy, and/or CT scan).
- g. ECOG PS must be verified prior to C1D1.
- h. Refer to [Table 4-2](#).
- i. On-trial imaging should be performed from the date of first dose, every 6 weeks (± 7 days) until Week 48, and every 12 weeks (± 7 days) thereafter until disease progression as assessed by the investigator, or until death, lost to follow-up, the start of new anticancer therapy, or withdrawal of consent, whichever occurs first. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts. If feasible, imaging should continue for subjects who discontinued treatment without radiographic PD.
- j. Only SAEs judged by the investigator as related to trial drug should be reported after the safety follow-up period has ended.
- k. Local safety labs (hematology and biochemistry) should be performed after completion of SBRT and within 72 hours before the start of C1D1 immunotherapy. On the other dosing days, local safety labs should be performed on the same day or within 72 hours prior to each dose.
- l. Baseline safety labs (hematology and biochemistry) should be done within 14 days of the first dose of SBRT. HBV and HCV testing at baseline should be done within 28 days of the first dose of SBRT.
- m. Coagulation is tested at screening only but can be tested during the trial per SOC for subjects on anticoagulant therapy or if clinically indicated as deemed by the investigator.
- n. Thyroid function tests (TSH, free T3, and free T4) should be measured at screening, C1D1, and on D1 of every other cycle (C3D1, C5D1, C7D1, etc). At other visits, thyroid function test consists of TSH only. However, if TSH is abnormal, reflexive testing of free T3 and free T4 is to be performed. TSH, free T3, and free T4 assessments should be performed at treatment discontinuation. If drug-related toxicity is present at treatment discontinuation, repeat the thyroid function assessments at the safety follow-up visits until resolution or follow-up is sufficient.
- o. For female subjects with reproductive potential, a serum pregnancy test (β -hCG) should be performed at screening (within 7 days of C1D1), and urine tests should be performed within 72 hours of Day 1 of each cycle, at the EOT visit, and at the 30-day safety follow-up visit. A urine test may be performed during an unscheduled visit at the investigator's discretion, if clinically indicated. If urine pregnancy test is positive, a serum pregnancy test is required to confirm.
- p. Imaging at screening must be done within 35 days of C1D1 (prior to biopsy and SBRT).
- q. PSA should be measured at screening and on Day 1 of every other cycle (Cycle 3, Cycle 5, Cycle 7, etc.).

Table 1-2 Schedule for PK, Cytokines, Immunophenotyping, and Immunogenicity (ADA) Samples – Dose Finding/Randomized Phase 2

Cycle/Visit	Screening	Cycle 1			Cycle 2			Cycle 3	≥ Cycle 4	Cycle 4	Unscheduled	End of Treatment	Post- Treatment Follow-up Visit ^a
Cycle Day	D -28 to D -1	D1	D8	D15	D1	D8	D15	D1	D1	D8			30d after last dose
Visit Window									+7d				+7d
		PK											
Before infusion (on infusion days)		X	X	X	X	X	X	X	X ^a	X	X ^b	X	X
End of infusion + 2 hours (±15 minutes)		X			X			X	X ^a				
		ADA											
Before infusion (on infusion days)		X			X			X	X ^a		X ^b	X	X
		Biomarker											
Cytokines/chemokines (soluble factors)		X	X	X	X	X	X	X	X ^e	X	X	X	
PBMCs (whole blood)		X	X	X	X	X	X	X	X ^e	X	X	X	
ctDNA (whole blood)	CCI												
TCR profiling (whole blood)		X		X	X		X ^d	X	X ^e		X	X	
IHC, DNA/RNA sequencing (tumor + TDLN biopsy) ^c	CCI												

Abbreviations: ADA=anti-drug antibody; ctDNA=circulating tumor deoxyribonucleic acid; D/d=day(s); DNA=deoxyribonucleic acid; IHC=immunohistochemistry; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic(s); RNA=ribonucleic acid; TCR=T-cell receptor; TDLN=tumor draining lymph node.

Note: All samples should be collected before the infusion on infusion days unless otherwise specified.

a. For PK and ADA samples, D1 of Cycle 4, Cycle 5, Cycle 7, and every 4 cycles thereafter (ie, Cycles 11, 15, etc).

b. Optional.

c. Recent biopsies from 1 radiation assigned and 1 non-radiation assigned lesion, must be collected during the screening period. The first on-treatment imaging assessment and on-treatment biopsy must be done between C2D15 and C3D1 where it is considered feasible without a risk of complications. The imaging assessment must be done prior to the biopsy.

d. Collect at same time of biopsy.

e. Biomarker samples should be collected on D1 of Cycle 5 and every cycle thereafter.

f. Optional.

2 INTRODUCTION

This is an open-label, phase 1/2 trial of GEN1042 (DuoBody®-CD40x4-1BB) aimed at evaluating the safety, abscopal effect, and antitumor activity of GEN1042 ± pembrolizumab following RT in subjects with metastatic solid tumors.

The trial includes a dose-finding part in part 1. Following enrollment and completion of the 27 Gy cohorts in part 1, the trial will be paused to evaluate the data from the 27 Gy cohorts. Based on the results from the analyses of the clinical, pharmacological, and translational data from the 27 Gy cohorts in part 1, the trial may resume with the 25 Gy cohorts and randomized phase 2 part, or the trial may be stopped following evaluation of the data. In the dose-finding part, following the initial RT administered to all trial subjects, a recommended dose of GEN1042 alone and in combination with pembrolizumab will be identified. If commenced, the randomized phase 2 part will further evaluate the selected dose of GEN1042 in monotherapy and GEN1042 in combination with pembrolizumab following RT, in selected metastatic solid tumors.

GEN1042 (BNT312) is being jointly developed by Genmab (Sponsor) and BioNTech, for treatment of solid malignant tumors following RT.

2.1 Trial Synopsis

Title	A Phase 1 Dose Finding and Phase 2 Randomized, Open-Label Trial to Evaluate the Safety and Clinical Activity of Immunoradiotherapy Combinations as a Treatment Option for Subjects with Metastatic Solid Tumors
Short Title	A Safety and Antitumor Activity Trial of Immunoradiotherapy Combinations as a Treatment Option for Subjects with Metastatic Solid Tumors
Clinical Phase	1/2
Purpose and Rationale	<p>GEN1042 is a bispecific antibody that crosslinks CD40 on antigen-presenting cells (APCs) with 4-1BB on activated T cells, thereby inducing conditional stimulation of and co-stimulatory activity on both cell types. In the context of cancer, GEN1042 is hypothesized to enhance antitumor immunity by crosslinking 4-1BB-positive, tumor-specific T cells with CD40-positive APCs in either the tumor-draining lymph nodes or intratumorally.</p> <p>The current body of clinical data suggests that the addition of checkpoint blockade following radiotherapy (RT) is safe. RT can generate an in-situ vaccine effect, therefore leading to dendritic cell (DC) activation and priming of antitumor T cells.</p> <p>Radiation can promote adaptive resistance through upregulation of PD-L1 on tumor cells, and the addition of checkpoint blockade can overcome this resistance mechanism and enhance the generation of abscopal responses. Through conditional activation of CD40 and 4-1BB, GEN1042, when combined with an anti-PD-1 monoclonal antibody (mAb) immediately after RT, is hypothesized to induce potent antitumor activity through enhanced tumor antigen release and DC licensing, T-cell priming, cytokine and chemokine production, and expansion and survival of antigen-experienced T cells.</p> <p>The purpose of this trial is to evaluate whether stereotactic body radiotherapy (SBRT) followed by immunotherapy (GEN1042 alone or in combination with pembrolizumab) results in an enhanced antitumor immune response in subjects with oligometastatic solid tumors.</p>

Objectives and Endpoints	OBJECTIVES	ENDPOINTS
	Primary	
	<ul style="list-style-type: none"> Part 1: To determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of GEN1042 administered alone or in combination with pembrolizumab following SBRT Part 2: to evaluate the abscopal response of GEN1042 ± pembrolizumab following SBRT 	<ul style="list-style-type: none"> Part 1: Dose-limiting toxicity (DLT) Part 2: Abscopal response in non-irradiated target lesions as assessed by investigator
	Secondary	
	<ul style="list-style-type: none"> To evaluate the antitumor activity of GEN1042 ± pembrolizumab following SBRT 	<ul style="list-style-type: none"> Objective response rate (ORR) in irradiated and non-irradiated tumor lesions as assessed by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Part 1 and 2) Duration of response (DOR) as assessed by investigator per RECIST v1.1 (Part 1 and 2) Disease control rate (DCR) (Part 1 and 2) Progression-free survival (PFS) as assessed by investigator per RECIST v1.1 (Part 1 and 2) One-year overall survival (OS) (Part 1 and 2) Abscopal response in non-irradiated target lesions as assessed by investigator (Part 1)
	<ul style="list-style-type: none"> To evaluate the safety and tolerability of GEN1042 ± pembrolizumab following SBRT 	<ul style="list-style-type: none"> Adverse events (AEs) and safety laboratory parameters based on the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0
	<ul style="list-style-type: none"> To characterize the pharmacokinetics (PK) and immunogenicity of GEN1042 ± pembrolizumab following SBRT 	<ul style="list-style-type: none"> PK parameters and anti-drug antibodies
	Exploratory	
	<ul style="list-style-type: none"> To assess potential biomarkers associated with clinical response/safety to GEN1042 ± pembrolizumab following SBRT To evaluate the antitumor activity of GEN1042 ± pembrolizumab following SBRT based on immune RECIST (iRECIST) criteria 	<ul style="list-style-type: none"> Tumor microenvironment characterization CCI Tumor characterization CCI Peripheral immune system activation CCI Antitumor activity, ie, reduction in tumor size according to iRECIST by investigator assessment

		<ul style="list-style-type: none"> Changes in circulating tumor-derived DNA CCI
Trial Design	<p>This is a phase 1/2, open-label trial evaluating the safety, clinical activity, and abscopal response to GEN1042 as monotherapy and in combination therapy with pembrolizumab following standard SBRT in subjects with selected metastatic solid tumors.</p> <ul style="list-style-type: none"> The trial consists of 2 parts: 1) a phase 1, GEN1042 dose finding part, with or without pembrolizumab, following 2 different SBRT regimens and 2) a phase 2 part during which trial subjects will randomly be assigned to receive GEN1042 either as monotherapy or in combination with pembrolizumab, in each instance following prior standard SBRT, provided combination therapy following SBRT investigated in part 1 is deemed safe. In both parts of the trial, cycle 1 day 1 (C1D1) is defined as the date of the first dose of GEN1042 ± pembrolizumab. One cycle lasts 21 days from D1. Image-guided SBRT to at least 50% of the lesions will be conducted as a standard palliative procedure intended also as a priming intervention throughout the week prior to C1D1. If there are lesions only in the liver, at least 1 lesion needs to be spared from irradiation for the abscopal response assessment. Otherwise, the largest lesion(s) should be irradiated, if possible. The GEN1042 ± pembrolizumab treatment must commence within 7 days after the last dose of SBRT, else the subject will be a screen failure. <p><u>Part 1 (Phase 1 Dose Finding)</u></p> <p>In this part, a modified 3+3 dose finding design will be used to evaluate the safety of GEN1042 ± pembrolizumab following standard SBRT. The primary objective of the dose-finding part of the trial is to determine the MTD/RP2D of GEN1042 alone (cohort 1) or with concurrent pembrolizumab (cohort 2) following SBRT by assessing the incidence of DLTs during the first 21 days of therapy.</p> <p>The trial will start with recruitment into cohort 1. Trial subjects will first receive standard SBRT at a dose of 27 Gy (3 × 9 Gy) followed by GEN1042 at a dose of 100 mg (DL1a). If 1 of the first 3 subjects receiving GEN1042 100 mg intravenously (IV) following 3 × 9 Gy SBRT (DL1a) experience a DLT, an additional 3 subjects will be treated at that dose level, and if a DLT occurs in 1/6 subjects, the trial will proceed to initiation of cohort 2. If ≥2 of the first 3 or 6 subjects experience a DLT, a lower GEN1042 dose of CCI (DL1b) will be initiated. CCI If no DLT occurs among the first 3 evaluable subjects of a cohort, the dosing regimen will be declared safe. At least 6 subjects will be treated at the selected RP2D of part 1 prior to commencing part 2.</p> <p>After the identification of the safe GEN1042 dose following the radiation regimen, enrollment into cohort 2 will begin, using a modified 3+3 design to evaluate the safety of adding pembrolizumab at the fixed dose of 200 mg IV to the GEN1042 and SBRT regimen identified in cohort 1, following the same rules as in cohort 1. CCI If no DLT occurs among the first 3 evaluable subjects of a cohort, the dosing regimen will be declared safe. At least 6 subjects will be treated at the selected RP2D in cohort 2 of part 1 prior to commencing part 2.</p> <p>Following enrollment and completion of the 27 Gy cohorts in part 1, the trial will be paused in order to evaluate the data from the 27 Gy cohorts. Based on the results from the analyses of the clinical, pharmacological, and translational data from the 27 Gy cohorts in part 1, the RP2D of GEN1042 ± pembrolizumab and the SBRT regimen determined during part 1 may be further evaluated in part 2 or the trial may be stopped following evaluation of the data.</p> <p>The 5 × 5 Gy SBRT (25 Gy) dose can start in parallel to the 27 Gy SBRT cohorts. GEN1042 will be administered at the 100 mg dose (DL2a) and will follow the same schema as the DL1a. The identified GEN1042 dose will then be tested in combination with</p>	

	<p>pembrolizumab (cohort 2). This combination of 25 Gy SBRT and immunotherapy is essentially being conducted to evaluate its safety.</p> <p>Once the safety and tolerability of SBRT 25 Gy together with GEN1042 ± pembrolizumab is established, this dose level will not proceed to part 2, unless the preceding SBRT 27 Gy followed by the GEN1042 ± pembrolizumab combination proves unsafe, as described above or has an unfavorable benefit:risk profile, in which case part 2 of the trial will proceed with 25 Gy SBRT and the RP2D of GEN1042 ± pembrolizumab. Thus, part 2 of the trial will have only 1 SBRT regimen, depending on the documented safety profile, as well as the evaluation of the clinical, pharmacological, and translational data from the 27 Gy cohorts in part 1. Other doses of RT and GEN1042 may also be considered if the trial is resumed.</p> <p>If single agent GEN1042 with SBRT proves tolerable, and combination immunotherapy (GEN1042 + pembrolizumab) with SBRT proves intolerable, part 2 of the trial may proceed as a single arm protocol with GEN1042 and SBRT.</p> <p><u>Part 2 (Randomized Phase 2)</u></p> <p>If commenced, part 2 is planned as a randomized trial aimed to evaluate the abscopal response to GEN1042 ± pembrolizumab, following SBRT based on the radiation dose and RP2D of GEN1042 determined in part 1. All eligible subjects will first undergo SBRT and then will be randomly assigned 1:1 to a cohort receiving GEN1042 or GEN1042 and pembrolizumab. All subjects will be treated until disease progression, unacceptable toxicity, or withdrawal of consent.</p>
Population and Sample Size	<p>Part 1: Up to 48 subjects may be enrolled</p> <p>Part 2: Up to approximately 40 subjects (approximately 20 subjects per arm, if appropriate)</p>
Key Inclusion Criteria	<p>Subjects must be ≥18 years of age; have measurable disease according to RECIST v1.1; life expectancy of >3 months; qualify for palliative SBRT; have Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1 at screening; and have adequate bone marrow, liver, coagulation, and renal function.</p> <p>For part 1 (dose finding):</p> <ul style="list-style-type: none"> • Subject must have a histologically confirmed non-central nervous system (CNS) solid tumor including colorectal cancer (CRC), non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), breast cancer, esophageal cancer, cervical cancer, anal cancer, pancreatic adenocarcinoma, prostate cancer, or squamous cell carcinoma of the head & neck (HNSCC). The subject must have disease that is metastatic and for which there is no available systemic standard therapy likely to confer clinical benefit, or not be a candidate for such available therapy and for whom, in the opinion of the investigator, experimental therapy may be beneficial. <p>For part 2 (randomized phase 2):</p> <ul style="list-style-type: none"> • Subject must have a histologically confirmed non-CNS solid tumor that is metastatic including NSCLC, CRC, breast cancer, and 1 to 3 of the tumors that had a signal of antitumor activity observed during the dose-finding part of this trial. Subjects must have received at least 1, but no more than 3, prior systemic treatment regimens including established standard of care (SOC) (maintenance treatment is considered part of 1 treatment line) for advanced/metastatic disease with documented progressive disease on or after last prior treatment. <p>For both part 1 and 2:</p> <ul style="list-style-type: none"> • For subjects with CRC, breast cancer, prostate cancer, and pancreatic cancer, where checkpoint inhibitor is not approved as SOC: Subject has not received prior therapy with an anti-programmed cell death protein 1 (PD-1), anti-programmed death-ligand 1 (PD-L1), anti-PD-L2 agent, or anti-CD40 agent, or with an agent directed to another stimulatory or co-inhibitory TCR (eg, cytotoxic T-lymphocyte-associated protein-4, OX 40, 4-1BB).

	<ul style="list-style-type: none"> For subjects with NSCLC, SCLC, TNBC, esophageal cancer, cervical cancer, anal cancer, or HNSCC: <ul style="list-style-type: none"> Subject is either immune checkpoint inhibitor (ICI) treatment naive OR Has been treated for at least 3 months with an approved anti-PD-1/anti-PD-L1/anti-CTLA4 mAb administered either as monotherapy, or in combination with chemotherapy Has demonstrated a radiographic disease progression during or after the last dose of ICI treatment, if applicable. <p>For subjects with HNSCC of oropharynx and cervical cancer, documentation of tumor human papillomavirus status is required (eg, p16 immunohistochemistry testing). Tests done on primary tumor specimens per local SOC are sufficient to meet this criterion.</p> <ul style="list-style-type: none"> Subjects must have at least 2 and no more than 6 separate extracranial lesions (including primary tumor if present), with each having a size of ≤ 5 cm. One lesion up to 10 cm in diameter is allowed if this lesion can be irradiated (all other lesions must have a size of ≤ 5 cm). <ul style="list-style-type: none"> At least 50% of lesions must be safely amenable to irradiation in the opinion of the treating radiation oncologist. This can be a lesion that was previously irradiated if prior radiation preceded projected first fraction of SBRT by at least 6 months. There is at least 1 measurable lesion (per RECIST 1.1 criteria) that can be spared from the RT field. A maximum of 3 metastases (of more than 1 cm) in any organ is allowed. However, the maximum allowed number of metastases is 6, of which no more than 3 metastases must be >1 cm. Other exceptions may be considered with sponsor consultation. If there are lesions only in the liver, at least 1 lesion needs to be spared from irradiation for the abscopal response assessment. Otherwise, the largest lesion(s) should be irradiated, if possible.
Key Exclusion Criteria	<ul style="list-style-type: none"> Subject has a history of other prior malignancy, with the exception of non-melanoma skin cancers and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, prostate, or breast, or has undergone potentially curative therapy with no evidence of disease recurrence for at least 3 years prior to the first trial treatment and no additional therapy is required or anticipated to be required during the trial period. Other exceptions may be considered with sponsor consultation. Subject discontinued prior ICI treatment due to grade 3 or higher immune-related AEs. Subject has had palliative or curative RT within 14 days prior to SBRT. Subject has any condition that is contraindicated to RT, such as connective tissue disorders with significant vasculitis (systemic lupus erythematosus or scleroderma), significant pre-existing lung disease if diffusing capacity is severely reduced in subjects requiring thoracic radiation, inflammatory bowel diseases in subjects where the gastrointestinal tract will receive RT, or presence of a pacemaker in the RT field. Subject has a rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating investigator. CNS is the only metastatic site or subject has known active or untreated CNS metastases and/or carcinomatous meningitis (regardless of clinical stability), or spinal cord compression. <p>Note: Subjects with previously diagnosed brain metastases may participate provided they are stable (without evidence of progression by imaging, using the identical imaging modality for each assessment, either magnetic resonance imaging or computed tomography scan, for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not used steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.</p>

	<ul style="list-style-type: none"> • Subject has an active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. • Subject has a 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. • Subject has had an allogeneic tissue/solid organ transplant. • Subject has a history of (non-infectious) pneumonitis that has required oral or IV steroids or currently has pneumonitis that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. • Subject has an active infection requiring systemic therapy. • Subject has contraindications to the use of pembrolizumab per local prescribing information. • Subject has received any treatment known to induce radiosensitization that finished within 5 elimination half-lives prior to the start of SBRT. Radiosensitizer treatments include (but are not limited to) chemotherapeutic agents (5-fluorouracil, gemcitabine, doxorubicin, docetaxel, vinorelbine, carboplatin, cisplatin, methotrexate, bleomycin, hydroxyurea), and radiation enhancement agents (eg, ErbB family receptor blockers, bevacizumab, any BRAF inhibitor, or MEK inhibitor), or any prior investigational agent with such clinically significant activity. • Subject is a female who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this trial or within 1 month after the last dose of GEN1042 or 4 months after the last dose of pembrolizumab. • Subject is a male whose partner plans to have a child with this male subject while enrolled in this trial or within 1 month after the last dose of GEN1042 or 4 months after the last dose of pembrolizumab. • Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol specified assessments. • Subject has a known history of human immune deficiency virus (HIV) infection (HIV 1/2 antibodies). • Subject has a positive test for hepatitis B virus (HBV) (defined as positive for hepatitis B surface antigen or HBV DNA) or hepatitis C virus (HCV) (defined as positive for HCV antibody or HCV RNA) per local standard, indicating acute or chronic infection. • Subject has received prior treatment with a live, attenuated vaccine within 30 days prior to initiation of GEN1042 ± pembrolizumab. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines that are not allowed. Experimental and/or non-authorized severe acute respiratory syndrome coronavirus 2 vaccinations are not allowed. • Subject has a history of ≥ grade 3 anaphylaxis to mAb therapy as well as known or suspected allergy or intolerance to any agent given during the course of this trial.
Trial Drug	GEN1042: administered IV on Dose Day 1 (DD1) of each 3-week treatment cycle (21 days).

	<p>Pembrolizumab: for combination therapy, GEN1042 will be administered first followed by pembrolizumab infusion on DD1 of each 3-week treatment cycle (21 days).</p> <p>Treatment administration in part 1 is shown below.</p> <table><tr><th>Dose Level</th><th>SBRT Fractionation</th><th>Cohort 1</th><th>Cohort 2</th></tr><tr><td>Dose Level 1a (DL1a)</td><td>RT1: 3 × 9 Gy</td><td>RT1 + GEN1042 100 mg</td><td>RT1 + GEN1042 100 mg + pembrolizumab 200 mg</td></tr><tr><td>Dose Level 1b (DL1b)</td><td>RT1: 3 × 9 Gy</td><td>RT1 + GEN1042 CCI</td><td>RT1 + GEN1042 CCI + pembrolizumab 200 mg</td></tr><tr><td>Dose Level 2a (DL2a)</td><td>RT2: 5 × 5 Gy</td><td>RT2 + GEN1042 100 mg</td><td>RT2 + GEN1042 100 mg + pembrolizumab 200 mg</td></tr><tr><td>Dose Level 2b (DL2b)</td><td>RT2: 5 × 5 Gy</td><td>RT2 + GEN1042 CCI</td><td>RT2 + GEN1042 CCI + pembrolizumab 200 mg</td></tr></table> <p>Note: GEN1042 and pembrolizumab are administered as IV infusions every 3 weeks. CCI</p> <p>RT will be given on alternate days for the 3 × 9 Gy scheme. For the 5 × 5 Gy scheme, RT will be given on consecutive weekdays (Monday to Friday). SBRT is expected to be completed in 7 days. Abbreviations: RT=radiotherapy; SBRT=stereotactic body radiotherapy.</p> <p>In part 2, subjects will be treated with GEN1042 alone or in combination with pembrolizumab, following SBRT based on the RP2D determined in part 1.</p>	Dose Level	SBRT Fractionation	Cohort 1	Cohort 2	Dose Level 1a (DL1a)	RT1: 3 × 9 Gy	RT1 + GEN1042 100 mg	RT1 + GEN1042 100 mg + pembrolizumab 200 mg	Dose Level 1b (DL1b)	RT1: 3 × 9 Gy	RT1 + GEN1042 CCI	RT1 + GEN1042 CCI + pembrolizumab 200 mg	Dose Level 2a (DL2a)	RT2: 5 × 5 Gy	RT2 + GEN1042 100 mg	RT2 + GEN1042 100 mg + pembrolizumab 200 mg	Dose Level 2b (DL2b)	RT2: 5 × 5 Gy	RT2 + GEN1042 CCI	RT2 + GEN1042 CCI + pembrolizumab 200 mg
Dose Level	SBRT Fractionation	Cohort 1	Cohort 2																		
Dose Level 1a (DL1a)	RT1: 3 × 9 Gy	RT1 + GEN1042 100 mg	RT1 + GEN1042 100 mg + pembrolizumab 200 mg																		
Dose Level 1b (DL1b)	RT1: 3 × 9 Gy	RT1 + GEN1042 CCI	RT1 + GEN1042 CCI + pembrolizumab 200 mg																		
Dose Level 2a (DL2a)	RT2: 5 × 5 Gy	RT2 + GEN1042 100 mg	RT2 + GEN1042 100 mg + pembrolizumab 200 mg																		
Dose Level 2b (DL2b)	RT2: 5 × 5 Gy	RT2 + GEN1042 CCI	RT2 + GEN1042 CCI + pembrolizumab 200 mg																		
Statistics	<p>In part 1, a modified 3+3 dose finding design is being used to determine the MTD of GEN1042 alone (cohort 1) or with concurrent pembrolizumab (cohort 2) following SBRT by assessing the incidence of DLTs during the first 21 days of therapy. Abscopal response in non-irradiated target lesions as assessed by investigator is the primary endpoint in part 2 and secondary endpoint in part 1. Abscopal response is defined as a reduction of at least 30% in diameter of the best responding non-irradiated target lesion. Abscopal response rate will also be calculated and is defined as the proportion of subjects with an abscopal response. Abscopal response rate/ORR and its exact 2-sided 95% confidence interval, using the Clopper Pearson method, will be presented by regimen (part 1) or treatment arm (part 2). DCR, defined as the proportion of subjects with a best overall response of complete response, partial response, and stable disease, will be summarized similar to ORR. The Kaplan-Meier method will be used to estimate the survival functions for DOR, PFS, and OS in each treatment arm. RECIST criteria 1.1 will be used to define response. AEs will be described using summary statistics. Clinical laboratory data will be presented in listings and shift tables.</p>																				
GCP Compliance	<p>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.</p>																				

2.2 Background

2.2.1 *Oligometastatic Disease Setting*

Metastatic disease is now considered to exist along a spectrum of virulence with a tumor's proclivity for distant spread determined by both host and tumor factors. Within this spectrum, a subset of patients will harbor metastases that are limited in number and location and meet the definitions of OMD ([Foster et al., 2020](#)). OMD is the umbrella term for all states of limited metastatic disease, ie, an intermediate state between localized and systemically metastasized disease, where radical local treatment of the primary cancer and all metastatic lesions might have a curative potential ([Hellman and Weichselbaum, 1995](#)). OMD is defined in most trials as 1 to 3 or 1 to 5 metastatic lesions ([Palma et al., 2014](#)). In addition, patients with OMD usually do not eventually progress to a widespread distribution of cancer ([Hellman and Weichselbaum, 1995](#)). However, while a select number of patients with OMD may survive beyond 5 years with systemic therapy, systemic therapy is rarely curative. The OMD paradigm suggest that treatment of these limited metastatic lesions may lead to long-term survival. Hence, there is an unmet medical need for better therapies for the majority of patients with OMD who eventually succumb to their disease.

2.2.1.1 *Role of Radiotherapy in the Treatment of OMD*

SBRT (also called SABR) is a method of external beam RT that accurately delivers a high dose of irradiation in 1 or few treatment fractions to an extracranial target ([Guckenberger et al., 2014](#)). SBRT has shown to be a successful treatment for tumors of the lung with sizes of ≤ 5 cm and can be given in doses varying up to 3×18 Gy ([Grills et al., 2010](#); [Palma et al., 2010](#)) with limited toxicity. SBRT can be safely used to treat small tissue volume and allows for precise therapy delivery that spares lymph nodes and bone marrow, critical in the context of radioimmunotherapy. Through multisite irradiation, tumoral heterogeneity may result in additional exposure of tumor-associated antigens, and certain organs may be more favorable in mounting an immune response than others ([Tang et al., 2017](#)). See Section 2.3.1 for further details.

Recent evidence demonstrates that loco-regional treatment with SBRT with curative intent is a good alternative as compared with conventional 3D RT for patients with solid tumors, with durable remissions and an acceptable toxicity profile. Many non-randomized trials have shown that SBRT for oligometastases is safe and effective, with local control rates of about 80% ([Salama and Milano, 2014](#)). For colorectal, non-small cell, and renal cell cancers, 1-year metastasis control rates ranged from 67 to 91% ([Salama and Milano, 2014](#)).

More recently, randomized phase 2 trials have shown the potential of metastasis-directed SBRT to improve survival of patients with OMD ([Gomez et al., 2019](#); [Iyengar et al., 2018](#); [Ost et al., 2018](#); [Palma et al., 2019](#); [Phillips et al., 2020](#)). In the majority of these trials, SBRT was well tolerated and seemed to provide the largest benefit to metastatic patients with low-volume disease. Of note, the SABR-COMET trial evaluated the effect of SABR when added to standard palliative care on survival, oncological outcomes, toxicity, and quality of life in patients with a controlled primary tumor and 1 to 5 oligometastatic lesions. In the SABR group, subjects received stereotactic radiation to all sites of metastatic disease, with the goal of achieving disease control while minimizing potential toxicities. In general, allowable SABR doses ranged from 30

to 60 Gy in 3 to 8 fractions, depending on target size and location. The subjects in the SABR group achieved a statistically significant doubling of PFS (HR 0.47, 95% CI: 0.30-0.76), with an insignificant improvement in OS, with an increased risk of toxicity, including a 4.5% risk of grade 5 toxicity assessed as related to SABR (Palma et al., 2019). It appears likely that the use of SABR to all lesions confers some risk and it may be possible to reduce toxicity by radiating select lesions and optimizing its use.

2.2.1.2 *Role of Immunotherapy in the Treatment of Metastatic Disease*

Immunotherapy is now well established as a treatment modality for a subset of patients with metastatic disease. Significant and clinically meaningful improvements in efficacy outcomes have been reported in patients with different solid tumors (NSCLC, melanoma, HNSCC, esophageal cancer, TNBC, urothelial cancer and few others) treated with CPIs alone or in combination with other therapies (Bavencio SmPC, 2020; Imfinzi SmPC; Keytruda SmPC, 2020; Opdivo SmPC; Tecentriq SmPC; Yervoy SmPC, 2016). Similar to the impact of metastasis-directed RT, the efficacy of immunotherapy seems the greatest in the setting of low-volume disease (Joseph et al., 2018). Moreover, recent data by Hutchinson et al. suggests that at least in TNBC, a more advanced disease is less immunogenic compared with primary cancer and this explains the lack of efficacy of ICIs in heavily pretreated patients (Hutchinson et al., 2020). The data demonstrated that in the transition from primary to metastatic disease, TNBCs treated with traditional chemotherapy regimens exhibited decreased immune activity over time. This was illustrated by decreased stromal tumor-infiltrating lymphocytes and decreased expression of immune activity-related gene signatures. These phenotypes may partially explain the limited efficacy of ICIs in heavily pre-treated patients in the metastatic TNBC setting and highlight the importance of their use instead in a setting of less advanced disease. There is other data supportive of this hypothesis coming from neo/adjuvant trials of different cancers (Eggermont et al., 2016; Zimmer et al., 2020).

OMD constitutes a disease stage of relatively low tumor burden in which the escape from immune control mechanisms has further progressed due to mechanisms described above. Therefore, it appears meaningful to build on potential synergy of SBRT and CPI in this context (for more details see Section 2.3.1). It is hypothesized that irradiation of several lesions can provide not only local control of the lesions, but, when given in combination with immunotherapy, can enable the destruction of tumors at anatomical locations far outside of the radiation field. Trials evaluating this concept are currently ongoing (for review see (Brooks and Chang, 2019)).

2.3 Trial Rationale

2.3.1 *Rationale for the Use of Immunotherapy Following SBRT*

The abscopal effect is the term used to describe tumor regression observed after radiation therapy in tumor lesions that are outside the radiation field, including metastatic sites (Postow et al., 2012). This effect is pronounced in the presence of an intact immune system (Stone et al., 1979). The NCI describes abscopal effect as the shrinking or disappearance of tumors in parts of the body that were not the direct target of local therapy, such as radiation therapy (NCI, 2020). The abscopal effect has been reported in several malignancies, including malignant melanoma and NSCLC (for review see (Craig et al., 2021; Jagodinsky et al., 2020)).

2.3.1.1 Mechanisms of Radiation-Induced Abscopal Effects

The abscopal effect is believed to occur via the ability of RT to affect the immune system and tumor microenvironment. This can occur through several mechanisms including the induction of immunogenic cell death and by modulation of immune checkpoints via radiation-induced signaling (for review see ([Zhao and Shao, 2020](#))). Radiation specifically promotes immunogenic cell death through the release of high mobility group box 1, ADP, and uric acid; by promoting the transport of calreticulin to the cell surface; and by increasing the expression of heat shock proteins and other substrates. The radiation-induced increase in protein breakdown also promotes loading and increased expression of MHC class I proteins on the tumor cell surface, potentially leading to the recognition of TAAs by cytotoxic T cells. Radiation also promotes the accumulation of DNA in the cytosol, leading to immune activation through the stimulator of interferon genes protein and cyclic GMP-AMP synthase pathways. After tumor cell death, the release of cell debris with associated danger signals (such as damage-associated molecular patterns, TAAs, and inflammatory cytokines activate APCs, such as DCs), and enables them to present the TAAs to cells of the immune system in draining lymph nodes. As a result, polyclonal TAA-specific cytotoxic T cells are primed to attack both tumor located within the radiation field and those in more distant locations.

2.3.1.2 Combination of Radiotherapy and Immunotherapy

The effects of radiation on the immune system provide a basis for the rational design of combination therapy with immune modulators and RT. In mice, Deng et al. demonstrated that PD-L1 was upregulated in the tumor microenvironment after RT ([Deng et al., 2014](#)). Moreover, administration of anti-PD-L1 enhanced the efficacy of IR through a cytotoxic T cell-dependent mechanism. Concomitant with IR-mediated tumor regression, IR and anti-PD-L1 synergistically reduced the local accumulation of tumor-infiltrating MDSCs, which suppress T cells and alter the tumor immune microenvironment. Finally, activation of cytotoxic T cells with combination therapy mediated the reduction of MDSCs in tumors through the cytotoxic actions of TNF ([Sagiv-Barfi et al., 2014](#)). Sagiv-Barfi et al also demonstrated in 5 patients receiving atezolizumab and radiation therapy, at least stabilization of systemic progression in all patients and a RECIST PR at systemic sites in 1 patient. Transient, grade 1-2 inflammatory AEs (fevers, flu-like symptoms) occurred with no serious immune-related toxicities ([Sagiv-Barfi et al., 2014](#)). Abscopal out-field effects of irradiation have also been described in addition to a reduction in circulating MDSCs in a melanoma patient treated with the anti CTLA-4 ipilimumab and RT ([Postow et al., 2012](#)).

In an earlier trial where RT was combined with GM-CSF in subjects with stable or progressing metastatic solid tumors with at least 3 measurable sites of disease, abscopal response occurred in 11 (26.8%, 95% CI 14.2-42.9) subjects. Subjects with larger tumor burdens (>6 lesions) had no abscopal response, whereas PRs and CRs were seen in subjects with lower disease burdens. More recently, a secondary analysis of KEYNOTE-001 showed increased efficacy of pembrolizumab in subjects with NSCLC who had previously received thoracic radiation ([Shaverdian et al., 2017](#)). In the seminal PACIFIC 3 trial, survival of subjects with locally advanced NSCLC was significantly improved with the addition of immunotherapy after completion of chemoradiotherapy ([Antonia et al., 2018](#)). In addition, subjects in the trial whose last dose of radiation was less than 14 days prior to randomization, derived more favorable OS benefit compared to those whose randomization was at least 14 days after last radiation (HR 0.42

[0.27 – 0.67] vs 0.81 [0.62-1.06]), further supporting the synergistic effect between radiation and immunotherapy ([Antonia et al., 2018](#)).

While the abscopal response has been documented in some studies, several prospective studies investigating the efficacy and safety of combining radio- and immunotherapy in the metastatic disease setting yielded inconclusive results (for review see ([Turchan et al., 2021](#))). This is most likely due to differences in design, including the number of metastases targeted with RT, its dose and fractionation, immunotherapy modality and timing, and also potential antagonistic effects of both therapies ([Turchan et al., 2021](#)). This data is somewhat in contrast to results obtained in large, placebo-controlled, randomized phase 3 trials in the adjuvant setting where administration of CPIs proved to be clinically significantly beneficial ([Antonia et al., 2018](#); [Gray et al., 2020](#); [Kelly et al., 2021](#)), leading to approval of durvalumab for stage III NSCLC following chemoradiation ([Imfinzi SmPC](#)) and for nivolumab for esophageal or GEJ cancer following neoadjuvant chemoradiotherapy ([Opdivo SmPC](#)). Further trials in perioperative and nonmetastatic setting are ongoing. Importantly, there have been no unexpected safety findings reported (for review see ([Hwang et al., 2018](#))).

2.3.2 Rationale for Evaluation of GEN1042 and GEN1042 in Combination with Pembrolizumab

2.3.2.1 Rationale for Development of GEN1042

GEN1042 is a bispecific antibody that crosslinks CD40 on APCs with 4-1BB on activated T cells, thereby inducing conditional stimulation of and co-stimulatory activity on both cell types. It is hypothesized that upon simultaneous binding of GEN1042 to CD40 on DCs and 4-1BB on T cells, the CD40-binding arm induces DC licensing through CD40 cross-linking, which together with cross-linking of 4-1BB by the other arm, leads to efficient, conditional T-cell activation. GEN1042 contains a silenced Fc region that does not bind to FcγRs or complement factor C1q, thereby preventing CD40 or 4-1BB agonist activity through FcγR-mediated cross-linking or cytotoxicity through Fc-mediated effector functions. The unique MoA of GEN1042 supports the premise that GEN1042 is a promising therapeutic agent with potential efficacy in many different cancer types.

Since resting T cells lack 4-1BB expression, T cells will only be activated by GEN1042 after TCR triggering. In the context of cancer, GEN1042 is hypothesized to enhance antitumor immunity by cross-linking 4-1BB-positive, tumor-specific T cells with CD40-positive APCs in either the tumor-draining lymph nodes or intratumorally.

For information related to the nonclinical studies for GEN1042, refer to the IB.

2.3.2.2 Rationale for Treatment with GEN1042 in Combination with Pembrolizumab

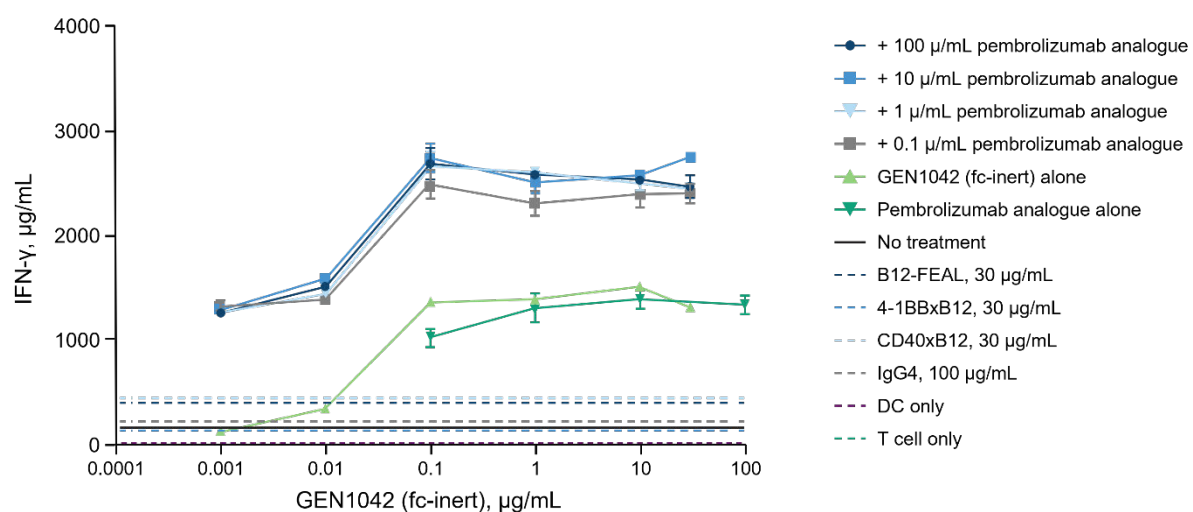
Since 4-1BB is often co-expressed on PD-1+ cells, blockade of PD-L1/PD-1 signals and co-stimulation through 4-1BB may synergize to enhance T-cell effector functions and improve the duration of the response ([Kim et al., 2019](#)). Through conditional activation of CD40 and 4-1BB, GEN1042, when combined with anti-PD-1 mAb immediately after RT, is hypothesized to induce potent antitumor activity through enhanced tumor antigen release and DC licensing, T-cell priming, cytokine and chemokine production, and expansion and survival of antigen-experienced T cells. The PD-(L)1 pathway is expected to be activated during priming as

well as during continuous antigen exposure, which may reduce the magnitude of the immune response induced by GEN1042, providing a rationale for the combination of GEN1042 with PD-1 blocking antibodies.

Pembrolizumab (Keytruda®) is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed death ligand 2 (PD-L2). Pembrolizumab is approved as monotherapy or in combination with other agents for a treatment of various solid tumors (eg, NSCLC, melanoma, urothelial cancer, esophageal cancer, kidney cancer, TNBC, liver cancer, HCC, HNSCC, cSCC, MSI-H/dMMR cancers) and is also in further clinical development for treatment of various malignancies at different disease stages (Keytruda SmPC, 2020).

MLR assays were performed in order to test the hypothesis that PD-1 blocking antibodies enhance the immune response induced by a CD40×4-1BB bispecific antibody in vitro (Figure 2-1). Concurrent incubation with GEN1042 and a pembrolizumab analog enhanced IFN- γ production compared to either GEN1042 or pembrolizumab analog monotherapy. The observed increase in IFN- γ in the combination treatment was dependent on the pembrolizumab analog concentration, as the highest fold changes (1.7x to 2.1x) of IFN- γ were observed at ≥ 1 $\mu\text{g/mL}$ pembrolizumab analog in combination with GEN1042 versus GEN1042 alone. These data suggest that the magnitude of immune response can be amplified through targeting of the PD-1/PD-L1 axis in combination with CD40 and 4-1BB.

Figure 2-1 In Vitro Potentiation of IFN- γ with Concurrent GEN1042 and α -PD-1 mAb



Abbreviations: DC=dendritic cell; ELISA=enzyme-linked immunoassay; IFN=interferon; LPS=lipopolysaccharide; MLR=mixed lymphocyte reaction; SD=standard deviation.

The capacity of PD-1 blocking antibodies to enhance the immune response induced by CD40×4-1BB bispecific antibodies was tested using a MLR assay with GEN1042. Unstimulated CD8+ T cells were co-cultured with allogeneic LPS-matured DCs in the presence of GEN1042 (0.001 – 30 $\mu\text{g/mL}$), pembrolizumab analog (0.1 – 100 $\mu\text{g/mL}$; research-grade) either alone or in combination for 5 days. Control groups consisting of nonspecific binding sequences (ie, B12), silencing mutations (FEAL) or similar Fc isotypes (IgG4) were evaluated at respective the top concentrations of GEN1042 and pembrolizumab treatment groups. Monocultures of DC and T cells were also evaluated. IFN- γ secretion was analyzed by ELISA. Data shown are mean IFN- γ $\pm$ SD of duplicate wells from 1 representative donor pair of 5 donor pairs (Study CCI).

2.3.3 Rationale for the Sequencing of SBRT and Immunotherapy and SBRT Dose and Fraction

2.3.3.1 Dose and Sequencing of SBRT and Immunotherapy

Earlier studies in mice that used the Armstrong strain of LCMV system were used for studying T-cell responses to viral infection ([Ahn et al., 2018](#); [Zhou et al., 2012](#)) and the kinetics of T-cell tumor infiltration following RT ([Frey et al., 2017](#); [Hettich et al., 2016](#)). In the LCMV model, the authors showed that the acute T-cell response is inhibited by endogenous PD-1 activity, but that anti-PD-L1 during initial T-cell activation increases granzyme B expression in virus-specific CD8 T-cells, resulting in decreased length of infection ([Ahn et al., 2018](#)). Following tumor irradiation with 12 Gy on 2 consecutive days, it was shown that overall leukocyte and CD8 T-cell frequencies peak at 5 days post-RT ([Hettich et al., 2016](#)). The highest effector to Treg ratio also occurred 5 days after RT, suggesting an ideal time point for checkpoint blockade therapy. Frey et al. showed that following 2×5 Gy fractions, CD8 T-cells peak at day 8 and decline significantly by day 9 while Treg have a bimodal peak on days 8 and 10 ([Frey et al., 2017](#)). These data show that checkpoint blockade therapy should soon follow RT to take advantage of the peak in tumor effector CD8 T cells.

Preclinical data suggest that CD40 activation can synergize with RT, and the most optimal RT delivery would be a hypofractionated schedule with single doses of at least 5 to 6 Gy ([Rech et al., 2018](#)). In case of CD40 activation in combination with radiation (a) the effect depends on T cells and BATF3 DCs, (b) the effect is independent of innate immune receptors such as STING or TLR, and (c) the addition of PD-1/PD-L1 and/or CTLA-4 mAb further enhances the effects of CD40/RT administration, but (d) the phenotype is lost if CD40 activation precedes RT ([Rech et al., 2018](#)).

In this current trial, SBRT will be utilized to irradiate several metastatic lesions, including those in the liver if present. The optimal fractionated regimen for augmenting immunogenicity of tumors in human subjects is unclear; therefore 2 fractionated regimens will be tested in this trial initially. Targeted focal radiation is currently planned as 9 Gy administered 3 times a week for a total of 27 Gy or 5 Gy administered 5 times a week for a total of 25 Gy. While both treatment regimens are within the range of regimens used for palliative radiation treatment and the difference of 2 Gy may appear small, these regimens differ significantly in the biologically effective dose of absorbed radiation ([Guerrero and Li, 2004](#)), and therefore may also appreciably differ in immunopotentiating effects.

Following SBRT, systemic immunotherapy will be administered constituting radioimmunotherapy regimen. For details see Section 4.3.

2.3.3.2 SBRT Dose and Fraction

Different total doses and fractionation schemes have been tested in pre-clinical models to maximize the abscopal effect ([Dewan et al., 2009](#); [Kulzer et al., 2014](#); [Lugade et al., 2005](#); [Schaue et al., 2012](#)). Taken together, these studies suggest that typically a high dose per fraction is needed for the abscopal effect. Moreover, the upregulation of checkpoint molecules can be induced in the tumor following RT and the level of induction is dependent on dose and fractionation ([Derer et al., 2016](#); [Dovedi et al., 2014](#)).

2.3.3.3 *Clinical Data*

Numerous clinical trials have evaluated the immune-stimulatory effects of RT ([Buchwald et al., 2018](#)). The majority of these trials use RT and immune checkpoint regimens based on the pre-clinical data. The data generated are consistent with preclinical results showing that sequential use of RT and immunotherapy, results in a more pronounced treatment effect.

2.3.4 *Rationale for Radiating at Least 50% of Lesions and Liver Lesions*

A previous strategy for using immunotherapy following SBRT in the metastatic setting was to apply RT to a single lesion before the start of immunotherapy, as an in vivo vaccination. In the PEMBRO-RT trial, subjects with metastatic NSCLC were treated with pembrolizumab either alone or after RT to a single tumor site. Results from the trial suggested benefit of such an approach as demonstrated by an increase in ORR, PFS and OS in the experimental arm ([Theelen et al., 2019](#)). However, the results between the control and experimental arm were not statistically significant and did not meet the trial's prespecified end point criteria for meaningful clinical benefit. More recently, in a randomized phase 2 trial investigating efficacy and safety of the administration of nivolumab with or without concurrent SBRT to a single lesion in subjects with metastatic HNSCC or WHO type I-III nasopharyngeal carcinoma, no statistically significant difference in ORR, OS, or PFS was observed between arms and no evidence of an abscopal effect was observed ([McBride et al., 2021](#)).

Another approach currently tested in several clinical trials explores a biological rationale for irradiating multiple tumor sites: through exploiting tumoral heterogeneity this may result in additional exposure of tumor-associated antigens. In that context certain organs may be more favorable in mounting an immune response than others: a recent phase 1 trial showed that liver irradiation was associated with greater systemic immune activation than lung irradiation ([Tang et al., 2017](#)). These findings are further supported by data demonstrating that patients with liver metastases had significantly less clinical benefit from immunotherapy, regardless of disease histology ([Yu et al., 2021](#)), in particular, the presence of liver metastases correlated with inferior PFS and OS in metastatic melanoma and NSCLC when adjusting for clinicopathologic features, including tumor burden, PD-L1 or performance status. Moreover, there is experimental data suggesting that liver metastasis may potentially alter systemic antitumor immunity. It was demonstrated that liver-directed RT reshaped the liver immune microenvironment, and thus restored immunotherapy efficacy in models of liver metastases ([Yu et al., 2021](#)).

In the current trial immunotherapy follows radiation to at least half of tumor sites; with the intent to also irradiate lesions in the liver and spare metastasis-free lymph nodes to determine local and abscopal effect of such intervention. This is in contrast to the SABR-COMET trial in which all metastatic lesions were radiated ([Palma et al., 2019](#)) and thus, is an attempt to optimize the use of SABR, allow for observation of the abscopal effect, and minimize toxicity.

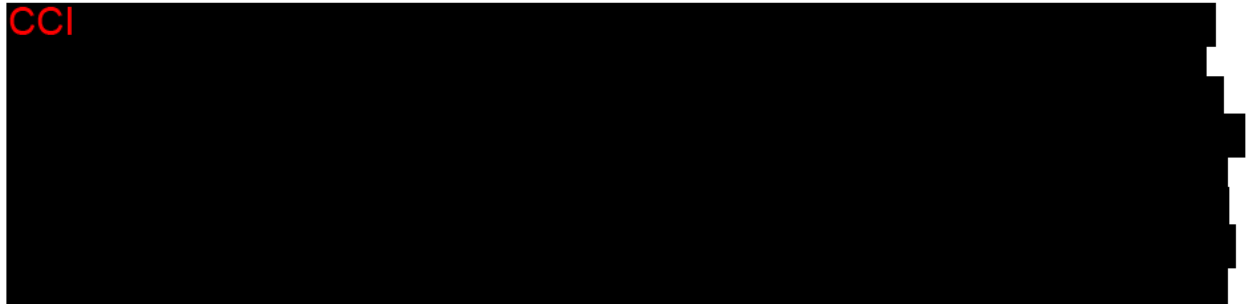
2.4 **Benefit-Risk Assessment**

2.4.1 *Potential Benefit*

Based on preclinical and clinical data and published data from other human 4-1BB and CD40 mAbs, as well as data from clinical trials investigating administration of immunotherapy after prior chemoradiation, the benefit-risk ratio is considered positive for this trial. Patients with

OMD, with limited treatment options and for whom the investigator agrees that clinical trial participation is appropriate may benefit from treatment with SBRT and subsequent administration of GEN1042 with or without pembrolizumab. Pembrolizumab is an established anticancer agent that is being evaluated in combination with RT in several clinical trials.

CCI



2.4.2 Potential Risks

2.4.2.1 GEN1042

Hepatic events (aspartate aminotransferase [AST]/alanine aminotransferase [ALT] elevations) are an identified risk for GEN1042; potential risks include neutrophil count decreased and pneumonitis. When GEN1042 is given in combination with pembrolizumab, there is a potential risk of hyperinflammatory syndrome (hemophagocytic lymphohistiocytosis [HLH] including macrophage activation syndrome [MAS]). The potential risks and mitigation strategies of treatment with GEN1042 monotherapy or in combination with pembrolizumab are summarized in [Table 2-1](#). This data includes available preliminary results from the ongoing GCT1042-01 trial. Also refer to Sections [6.6.2](#) and [6.6.3](#) for dose modification and AE management guidance. Refer to the GEN1042 IB for further details.

In addition, the sponsor, together with the investigators will continuously monitor study subjects' safety throughout the trial as described in [10.1.10.3](#).

Table 2-1 GEN1042 Risk Mitigation Strategy

Identified Risk	Mitigation Strategy
Hepatic events (AST/ALT elevations)	Prevention: <ul style="list-style-type: none"> Per inclusion criteria: ALT and AST $\leq 1.5 \times \text{ULN}$. Additional requirement: Total bilirubin $\leq \text{ULN}$, except subjects with Gilbert's Syndrome, who must have a total bilirubin $\leq 3 \text{ mg/dL}$ and direct bilirubin $\leq \text{ULN}$. Per exclusion criteria: Subjects with a history of liver disease (eg, alcoholic hepatitis or nonalcoholic steatohepatitis, drug-related or autoimmune hepatitis) are excluded from participation. Management: Refer to Table 6-1 .
Potential Risks	Mitigation Strategy
Neutrophil count decreased	Prevention: Inclusion criterion requires ANC $\geq 1.5 \times 10^9/\text{L}$. Management: Refer to Section 6.6.2.1 for general guidance regarding managing clinically significant AEs.
Pneumonitis	Prevention: Per exclusion criteria: Subjects with a history of noninfectious pneumonitis who have required steroids or currently have pneumonitis are excluded from participation. Management: Refer to Table 6-1 .
Hyperinflammatory syndrome (HLH/MAS) when GEN1042 is used in combination with pembrolizumab	Prevention: <ul style="list-style-type: none"> Per inclusion criteria for combination therapy: No prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD40 or 4-1BB). Per inclusion criteria for combination therapy: Subject must have adequate organ and bone marrow function. Management: Refer to 10.9 (HLH-2004 diagnostic criteria and management guidelines).

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CD40=cluster of differentiation 40; CTLA-4=cytotoxic T-lymphocyte associated protein 4; HLH=hemophagocytic lymphohistiocytosis; MAS=macrophage activation syndrome; PD-1=programmed cell death protein 1; PD-L1/2= programmed death-ligand 1/2; ULN=upper limit of normal.

2.4.2.2 Pembrolizumab

Please refer to the current prescribing information of pembrolizumab for information about associated potential risks.

2.4.2.3 Radiation Toxicity

The effects of RT on nonmalignant tissues and the incidence and severity of toxicities are dependent on the specific anatomical site that is irradiated, the presence of comorbid conditions, the volume of tissue treated, and the radiation dose and fractionation. The key strategies involve reducing the level of radiation delivered to organs at risk by using SBRT, and the clinical management of radiation-induced toxicities once they occur, which is a standard medical practice. Data from recent randomized phase 2 trials investigating efficacy and safety of RT (vs no radiation) preceding immunotherapy did not reveal differences in grade ≥ 3 treatment-related toxicities between trial arms ([McBride et al., 2021](#); [Theelen et al., 2019](#)); for review see ([Hwang et al., 2018](#)). More recently, results from a pooled analysis of data from 68 prospective trials showed similar rates of AEs and no meaningful increase in serious AEs in subjects receiving an

ICI within 90 days following RT versus those who had not received prior RT ([Anscher et al., 2022](#)).

Systemic radiation injury is linked usually with total/subtotal body radiation, which will not be pursued in this trial. SBRT will be designed to ensure assigned dose is delivered to the target while not exceeding normal tissue constraints.

2.4.2.4 Potential Risks from Combination Therapy

Both GEN1042 and pembrolizumab are immunomodulatory agents. Therefore, the most likely anticipated overlapping toxicities with GEN1042 and pembrolizumab include irAEs, fatigue, IRR, and AST/ALT elevations.

2.4.3 Conclusion

In conclusion, the benefit/risk profile for treatment with RT, GEN1042 monotherapy, or in combination with pembrolizumab remains favorable. For the most up-to-date safety information for GEN1042, please refer to the current version of the IB. Refer to [Table 2-1](#) for risk mitigation strategies for GEN1042 and Sections [6.6.2](#) and [6.6.3](#) for toxicity management.

3 OBJECTIVES AND ENDPOINTS

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

Table 3-1 Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Primary	
<ul style="list-style-type: none"> Part 1: To determine the MTD and/or RP2D of GEN1042 administered alone or in combination with pembrolizumab following SBRT Part 2: To evaluate the abscopal response of GEN1042 ± pembrolizumab following SBRT 	<ul style="list-style-type: none"> Part 1: DLT Part 2: Abscopal response in non-irradiated target lesions as assessed by investigator
Secondary	
<ul style="list-style-type: none"> To evaluate the antitumor activity of GEN1042 ± pembrolizumab following SBRT 	<ul style="list-style-type: none"> ORR in irradiated and non-irradiated tumor lesions as assessed by investigator per RECIST v1.1 (Part 1 and 2) DOR as assessed by investigator per RECIST v1.1 (Part 1 and 2) DCR (Part 1 and 2) PFS as assessed by investigator per RECIST v1.1 (Part 1 and 2) One-year OS (Part 1 and 2) Abscopal response in non-irradiated target lesions as assessed by investigator (Part 1)
<ul style="list-style-type: none"> To evaluate the safety and tolerability of GEN1042 ± pembrolizumab following SBRT 	<ul style="list-style-type: none"> AEs and safety laboratory parameters based on the NCI-CTCAE v5.0
<ul style="list-style-type: none"> To characterize the PK and immunogenicity of GEN1042 ± pembrolizumab following SBRT 	<ul style="list-style-type: none"> PK parameters and ADAs
Exploratory	
<ul style="list-style-type: none"> To assess potential biomarkers associated with clinical response/safety to GEN1042 ± pembrolizumab following SBRT To evaluate the antitumor activity of GEN1042 ± pembrolizumab following SBRT based on iRECIST criteria 	<ul style="list-style-type: none"> Tumor microenvironment characterization CCI Tumor characterization CCI Peripheral immune system activation CCI Antitumor activity, ie, reduction in tumor size according to iRECIST by investigator assessment Changes in ctDNA CCI

Abbreviations: ADA=anti-drug antibody; ctDNA=circulating tumor-derived DNA; DCR=disease control rate; DLT=dose-limiting toxicity; DNA=deoxyribonucleic acid; DOR=duration of response; iRECIST=Immune Response Evaluation Criteria in Solid Tumors; MTD=maximum tolerated dose; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic(s); RECIST=Response Evaluation Criteria in Solid Tumors; CCI; RP2D=recommended phase 2 dose; SBRT=stereotactic body radiotherapy.

4 TRIAL DESIGN

4.1 Description of Trial Design

This is a phase 1/2, open-label trial evaluating the safety, clinical activity, and abscopal response to GEN1042 as monotherapy and in combination therapy with pembrolizumab following standard SBRT in subjects with selected metastatic solid tumors.

- The trial consists of 2 parts: 1) a phase 1, GEN1042 dose finding part, with or without pembrolizumab, following 2 different SBRT regimens, and 2) a phase 2 part during which trial subjects will randomly be assigned to receive GEN1042 either as monotherapy or in combination with pembrolizumab, in each instance following prior standard SBRT, provided combination therapy following SBRT investigated in part 1 is deemed safe.
- In both parts of the trial, C1D1 is defined as the date of the first dose of GEN1042 ± pembrolizumab. One cycle lasts 21 days from D1. Image-guided SBRT to at least 50% of the lesions will be conducted as a standard palliative procedure intended also as a priming intervention throughout the week prior to C1D1. If there are lesions only in the liver, at least 1 lesion needs to be spared from irradiation for the abscopal response assessment. Otherwise, the largest lesion(s) should be irradiated, if possible.
- The GEN1042 ± pembrolizumab treatment must commence within 7 days after the last dose of SBRT, else the subject will be a screen failure.

4.1.1 Part 1 (Phase 1 Dose Finding)

In the current study, at least 50% of tumor lesions will receive radiation and the remaining tumor site(s) will not be radiated in order to properly assess the abscopal effect (Section 6.1.2). However, collective results from evolving published data suggest that the abscopal effect is uncommon (Table 4-1). Therefore, based on the totality of data generated since the protocol has been written, the sponsor has decided to complete part 1 of the trial with the 27 Gy cohorts. After completion of the 27 Gy cohorts in part 1, available data will be analyzed. Based on these analyses, a decision on whether to resume the 25 Gy cohorts and part 2 of the trial or stop the trial will be made.

Table 4-1 Clinical Trials Assessing Abscopal Response Combining Checkpoint Inhibitors With Radiation Therapy

Indication/ Checkpoint Inhibitor	Phase n	Control Arm	Number of Lesions Irradiated	Gy Fraction	Response Endpoints	Reference
mNSCLC						
Pembrolizumab	2 randomized n=76	Pembrolizumab	1	8 Gy 3 fractions	ORR at Week 12 36% vs 18%* PFS 6.6m vs 1.9m * OS 15.9m vs 7.6m * Primary endpoints not met for each individual trial; therefore, pooled analysis results are not statistically valid.	(Theelen et al., 2019)
Pembrolizumab	1/2 randomized n=100	Pembrolizumab	1-4	SBRT 50 Gy 4 fractions Traditional RT 45 Gy 15 fractions	Overall ORR 22% vs 25%* Primary endpoint not met.	(Welsh et al., 2020)
Durvalumab/ tremelimumab	2 randomized n=90	Durvalumab/ tremelimumab	1-2	Low dose: 0.5 Gy bid over 2 days in Cycles 1-4 or hypofractionated: 24 Gy 3 fractions	ORR non-irradiated lesions 7.7% low-dose and 11.5% hypo-fractionated vs 11.5%* Study stopped for futility.	(Schoenfeld et al., 2022)
mRCC						
Nivolumab	2 n=69	Historical control for Nivolumab	1	10 Gy 3 fractions	ORR (25% nivolumab alone) ORR on irradiated lesions 29% ORR on non-irradiated lesion 12% No evidence of abscopal effect.	(Masini et al., 2022)
mHNSCC						
Nivolumab	2 randomized n=62	Nivolumab	≥1 (min)	27 Gy 3 fractions	ORR non-irradiated lesions 29.0% vs 34.5%* Primary endpoint not met.	(McBride et al., 2021)
Solid tumors						
CPI per SOC	2 randomized n=96	ICI alone	≤3 (max)	24 Gy 3 fractions	PFS 4.4m vs 2.8m* OS 14.3m vs 11.0m*	(Spaas et al., 2023)

Indication/ Checkpoint Inhibitor	Phase n	Control Arm	Number of Lesions Irradiated	Gy Fraction	Response Endpoints	Reference
					Abscopal response rate not reported. Primary endpoint not met.	

Abbreviations: bid=twice weekly; CPI=checkpoint inhibitor; HNSCC=squamous cell carcinoma of the head and neck; ICI=immune checkpoint inhibitor; m=month; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RCC=renal cell carcinoma; RT=radiotherapy; SBRT=stereotactic body radiotherapy; SOC=standard of care.

*Not statistically significant.

Bolded numbers indicate results from the radiotherapy combination arms.

Part 1 will enroll up to 48 subjects who have been diagnosed with solid tumors as specified by the inclusion criteria (Section 5.1) and for whom there is no available standard therapy likely to confer clinical benefit, as per inclusion criteria.

In this part, a modified 3+3 dose finding design will be used to evaluate the safety of GEN1042 ± pembrolizumab following standard SBRT. The primary objective of the dose-finding part of the trial is to determine the MTD/RP2D of GEN1042 alone (cohort 1) or with concurrent pembrolizumab (cohort 2) following SBRT by assessing the incidence of DLTs during the first 21 days of therapy.

The trial will start with recruitment into cohort 1 (Figure 4-1). Trial subjects will first receive standard SBRT at a dose of 27 Gy (3×9 Gy) followed by GEN1042 at a dose of 100 mg (DL1a) (Table 4-2). Once the planned number of DLT-evaluable subjects at the first dose level is reached, representatives of the sponsor and investigators, collectively forming the DEC, will together assess safety and determine whether initiation to cohort 2 can begin or a lower dose of GEN1042 is needed. The sponsor's internal SC may also be consulted. Additional details regarding the DEC and SC can be found in 10.1.

If 1 of the first 3 subjects receiving GEN1042 100 mg IV following 3×9 Gy SBRT (DL1a) experience a DLT, an additional 3 subjects will be treated at that dose level, and if a DLT occurs in 1/6 subjects, the trial will proceed to initiation of cohort 2. If ≥ 2 of the first 3 or 6 subjects experience a DLT, a lower GEN1042 dose of CCI (DL1b) will be initiated (Table 4-2). CCI If no DLT occurs among the first 3 evaluable subjects of a cohort, the dosing regimen will be declared safe. At least 6 subjects will be treated at the selected RP2D of part 1 prior to commencing part 2.

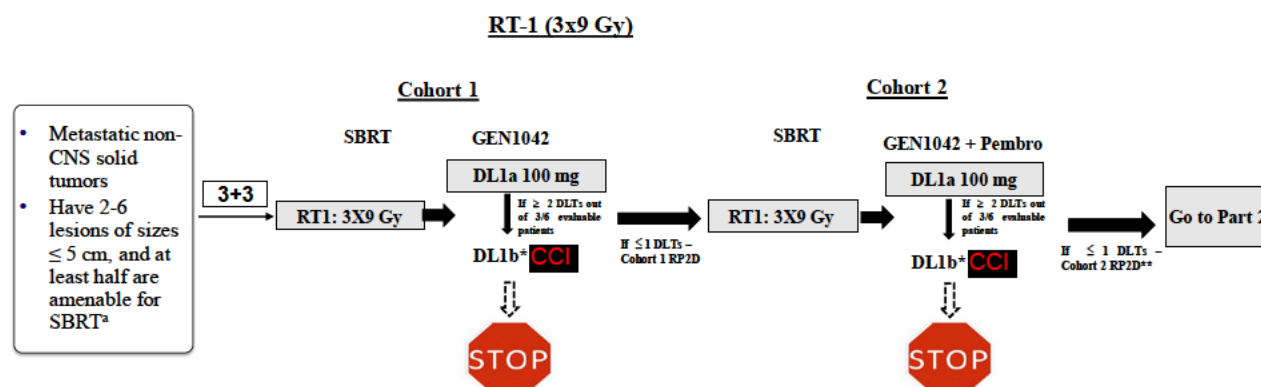
After the identification of the safe GEN1042 dose following the radiation regimen, enrollment into cohort 2 will begin, using a modified 3+3 design to evaluate the safety of adding pembrolizumab at the fixed dose of 200 mg IV to the GEN1042 and SBRT regimen identified in cohort 1. Once the planned number of DLT-evaluable subjects is reached in cohort 2, the DEC will assess safety in consultation with the SC and will review the DLT and overall safety data. If 1 of the first 3 subjects receiving pembrolizumab 200 mg IV with GEN1042 following SBRT experience a DLT, an additional 3 subjects will be treated, and if DLT occurs in 1/6, this regimen will be the RP2D for the pembrolizumab combination arm, and the trial will proceed to part 2. If ≥ 2 of the first 3 or 6 subjects experience a DLT, a lower dose of GEN1042 (DL1b) with pembrolizumab combination dose finding will commence. CCI If no DLT occurs among the first 3 evaluable subjects of a cohort, the dosing regimen will be declared safe. At least 6 subjects will be treated at the selected RP2D in cohort 2 of part 1 prior to commencing part 2.

Following enrollment and completion of the 27 Gy cohorts in part 1, the trial will be paused in order to evaluate the data from the 27 Gy cohorts. Based on the results from the analyses of the clinical, pharmacological, and translational data from the 27 Gy cohorts in part 1, the RP2D of GEN1042 ± pembrolizumab and the SBRT regimen determined during part 1 may be further evaluated in part 2 or the trial may be stopped following evaluation of the data.

Figure 4-1 Schematic Overview of the Trial – Part 1, RT-1 (3 × 9 Gy)

Part 1- Phase I Dose Finding

RT + GEN1042 +/- αPD-1 (Pembro) in Oligometastatic Solid Tumors



Note: DL1a & DL1b is for GEN1042 100 mg and CCI Q3W, respectively. Pembrolizumab will be given at 200 mg Q3W. Abbreviations: CNS=central nervous system; DL=dose level; DLT=dose-limiting toxicity; Pembro=pembrolizumab; Q3W=every 3 weeks; RP2D=recommended phase 2 dose; RT=radiotherapy; SBRT=stereotactic body radiotherapy.

a. One lesion up to 10 cm in diameter is allowed if this lesion can be irradiated (all other lesions must have a size of ≤ 5 cm).

*CCI

The 5 × 5 Gy SBRT (25 Gy) dose (Figure 4-2) can start in parallel to the 27 Gy SBRT cohorts. GEN1042 will be administered at the 100 mg dose (DL2a) and will follow the same schema as the DL1a (Table 4-2). The identified GEN1042 dose will then be tested in combination with pembrolizumab (cohort 2). This combination of 25 Gy SBRT and immunotherapy is essentially being conducted to evaluate its safety.

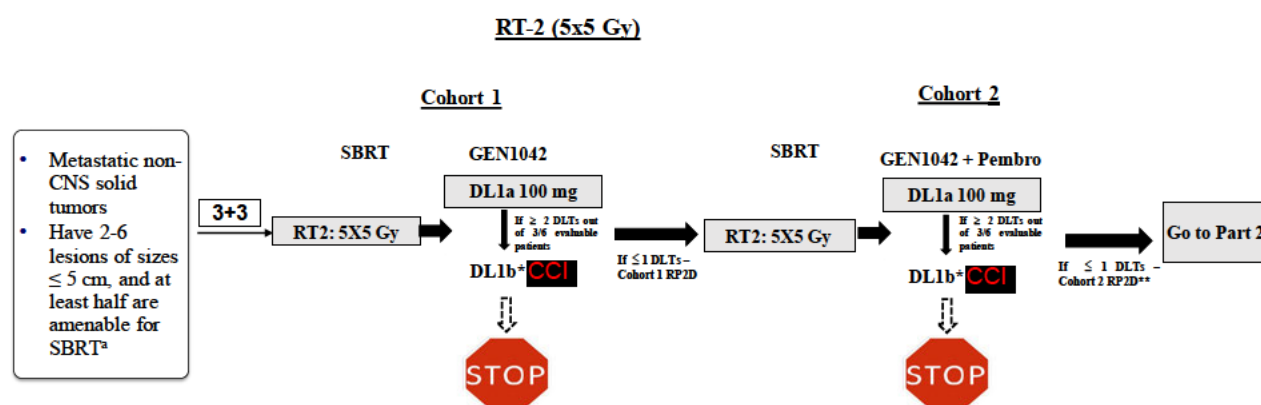
Once the safety and tolerability of SBRT 25 Gy together with GEN1042 ± pembrolizumab is established, this dose level will not proceed to part 2, unless the preceding SBRT 27 Gy followed by the GEN1042 ± pembrolizumab combination proves unsafe, as described above or has an unfavorable benefit:risk profile, in which case part 2 of the trial will proceed with 25 Gy SBRT and the RP2D of GEN1042 ± pembrolizumab. Thus, part 2 of the trial will have only 1 SBRT regimen, depending on the documented safety profile, as well as the evaluation of the clinical, pharmacological, and translational data from the 27 Gy cohorts in part 1. Other doses of RT and GEN1042 may also be considered if the trial is resumed.

If single agent GEN1042 with SBRT proves tolerable, and combination immunotherapy (GEN1042 + pembrolizumab) with SBRT proves intolerable, part 2 of the trial may proceed as a single arm protocol with GEN1042 and SBRT.

Figure 4-2 Schematic Overview of the Trial – Part 1, RT-2 (5 × 5 Gy)

Part 1- Phase I Dose Finding

RT + GEN1042 +/- αPD-1 (Pembro) in Oligometastatic Solid Tumors



Note: DL1a & DL1b is for GEN1042 100 mg and CCI Q3W, respectively. Pembrolizumab will be given at 200 mg Q3W. Abbreviations: CNS=central nervous system; DL=dose level; DLT=dose-limiting toxicity; Pembro=pembrolizumab; Q3W=every 3 weeks; RP2D=recommended phase 2 dose; RT=radiotherapy; SBRT=stereotactic body radiotherapy.

a. One lesion up to 10 cm in diameter is allowed if this lesion can be irradiated (all other lesions must have a size of ≤5 cm).

Table 4-2 Treatment Administration in Part 1

Dose Level	SBRT Fractionation	Cohort 1	Cohort 2
Dose Level 1a (DL1a)	RT1: 3 × 9 Gy	RT1 + GEN1042 100 mg	RT1 + GEN1042 100 mg + pembrolizumab 200 mg
Dose Level 1b (DL1b)	RT1: 3 × 9 Gy	RT1 + GEN1042 CCI	RT1 + GEN1042 CCI + pembrolizumab 200 mg
Dose Level 2a (DL2a)	RT2: 5 × 5 Gy	RT2 + GEN1042 100 mg	RT2 + GEN1042 100 mg + pembrolizumab 200 mg
Dose Level 2b (DL2b)	RT2: 5 × 5 Gy	RT2 + GEN1042 CCI	RT2 + GEN1042 CCI + pembrolizumab 200 mg

Note: GEN1042 and pembrolizumab are administered as IV infusions every 3 weeks. CCI

RT will be given on alternate days for the 3 × 9 Gy scheme. For the 5 × 5 Gy scheme, RT will be given on consecutive weekdays (Monday to Friday). SBRT is expected to be completed in 7 days.

Abbreviations: RT=radiotherapy; SBRT=stereotactic body radiotherapy.

4.1.2 Part 2 (Randomized Phase 2)

If commenced, part 2 may consist of approximately 40 subjects (approximately 20 subjects per arm) with non-CNS solid tumors that are metastatic, including NSCLC, CRC, breast cancer, and

1 to 3 of the tumor types that had a signal of antitumor activity observed during the dose finding part of this trial. Subjects must have received at least 1 but no more than 3 prior systemic treatment regimens including established SOC (maintenance treatment is considered part of 1 treatment line) for metastatic disease with documented PD on or after last prior treatment. For detailed inclusion/exclusion criteria, please refer to Section 5.

Part 2 will evaluate the abscopal response to GEN1042 alone and in combination with pembrolizumab, following SBRT based on the RP2D determined in part 1 (Figure 4-3).

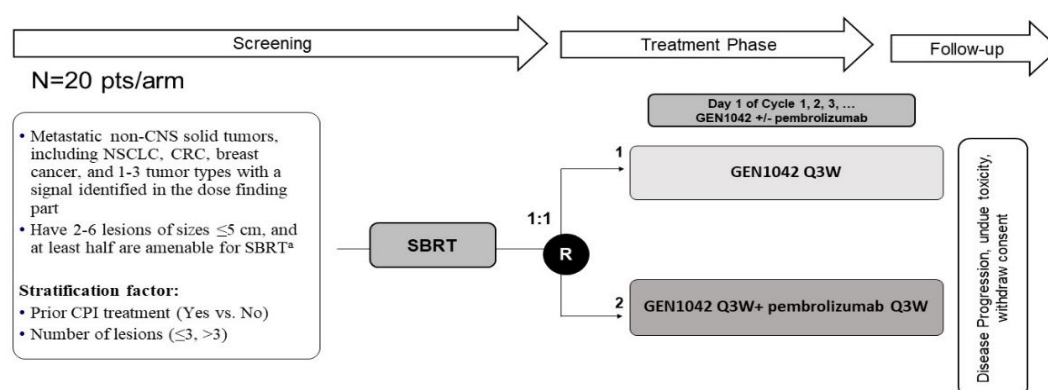
Assessments will be performed as detailed in the Schedule of Activities, Section 1.2.

Treatment will continue until at least 1 of the treatment discontinuation criteria is met (refer to Section 7.1). Subjects will be stratified by prior CPI treatment (yes vs no) and number of lesions (≤ 3 vs > 3).

Figure 4-3 Schematic Overview of the Trial – Part 2

Part 2 Randomized Phase 2

RT + GEN1042 +/- (Pembro) in Oligometastatic Solid Tumors



Note: SBRT schedule is identified during part 1.

Abbreviations: CNS=central nervous system; CPI=checkpoint inhibitor; CRC=colorectal cancer; NSCLC=non-small cell lung cancer; pts=patients; Pembro=pembrolizumab; Q3W=every 3 weeks; R=randomized; RT=radiotherapy; SBRT=stereotactic body radiotherapy.

a. One lesion up to 10 cm in diameter is allowed if this lesion can be irradiated (all other lesions must have a size of ≤ 5 cm).

4.1.3 Patient Input into Design

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

4.2 Trial Design Rationale

The trial consists of a dose finding part, and a randomized phase 2 part. The primary aim of the dose-finding part is to identify a safe and tolerable dose of GEN1042 with and without pembrolizumab, administered following SBRT. Two different SBRT regimens and GEN1042 dose schemes using a modified 3+3 design were selected.

In part 2, subjects will be randomly assigned to receive GEN1042 as monotherapy at the RP2D or in combination with pembrolizumab after safety has been established, and in both instances after an SBRT dose regimen is selected in part 1 of the trial. If part 2 commences, in case both

monotherapy and combination regimens are tested in phase 2, subjects may be randomly allocated to the respective trial arms. The aim of phase 2 is to evaluate the rate of abscopal response defined as RT-induced immune-mediated measurable tumor lesion regression at the non-irradiated cancer sites. Further, this part shall provide data on safety, tolerability, PK, and biomarkers of the selected GEN1042 dose in specific tumor types, and potential correlations to efficacy.

4.2.1 Rationale for 3+3 Design in Dose Finding Part

The 3+3 method was developed in the era of cytotoxic drugs, during which time it was assumed that both efficacy and toxicity increase with dose. Consequently, these methods have used toxicity as the primary endpoint (Le Tourneau et al., 2009; Rogatko et al., 2007). In the era of cancer immunotherapy, studies of agents usually have a wide therapeutic window with less and sometimes delayed toxicity (Le Tourneau et al., 2009). Evaluating safety findings during the first cycle in the cohort of 3 subjects treated at the predefined dose level and a safety margin of maximum 1/3 subjects with a DLT event provides sufficient margin to identify risks also for the regimens used in this trial.

According to a meta-analysis of 3,526 patients for toxicity and response patterns with immunotherapy combinations, anti-PD-1/PD-L1 CPIs can be safely given with a variety of other immunotherapy and targeted agents (Nikanjam et al., 2017). For the combination of immunotherapies, there were 23 trials in which the second drug was also an immunotherapy (8 combinations; 1,181 patients). All 2-drug combinations of exclusively immunotherapy had acceptable safety profiles providing that the dose of ipilimumab was lowered, which is not surprising as ipilimumab has the least tolerable profile among the approved CPIs. GEN1042 has a favorable safety profile based on the monotherapy dose escalation part of the ongoing GCT1042-01 trial. Among 10 dose levels tested from 0.1 mg to 400 mg in the Phase 1 dose escalation, there has been only 1 DLT (1/6, 16.7%) of increased transaminases at the 200 mg dose level. The MTD has not been reached, demonstrating a broad safety range (Johnson et al., 2021). No DLTs have been reported in the combination part of the trial.

4.3 Dose and Schedule Rationale

4.3.1 GEN1042

CCI

- CCI
- CCI

- CCI [REDACTED]
- CCI [REDACTED]

CCI [REDACTED]

Dose and dosage schedule of pembrolizumab used in this current trial corresponds with the current label for all the approved indications, both as monotherapy and in combination with other agents. There are 2 randomized phase 2 trials suggesting that standard dose pembrolizumab can be safely combined with SBRT ([Maity et al., 2018](#); [Theelen et al., 2019](#)).

4.3.2 Pembrolizumab

For subjects receiving GEN1042 + pembrolizumab combination therapy, pembrolizumab will be dosed at 200 mg Q3W (ie, on Day 1 of each treatment cycle), consistent with the pembrolizumab prescribing information.

4.4 Estimated Trial Duration and End of Trial Definitions

4.4.1 Estimated Trial Duration for an Individual Subject

The estimated trial duration for an individual subject is about 2 years, consisting of a 28-day screening period, an estimated 18-week treatment period (the duration of treatment may vary for each subject), a 90-day post-treatment safety follow-up period, and an estimated 1-year survival follow-up period (the duration of follow-up may vary for each subject).

A subject is considered to have completed the trial if the subject has completed all periods of the trial including the last overall survival contact shown in the Schedule of Activities (Section [1.2](#)).

4.4.2 End of Trial and Estimated Trial Duration

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

In this trial, the end of trial will occur a maximum of 2 years after the first dose of the last subject enrolled.

Availability of trial treatment after the end of the trial is covered in Section [6.7](#).

5 TRIAL POPULATION

The inclusion and exclusion criteria for enrolling subjects in this trial are described below.

NOTE: Investigators should ensure that all trial enrollment criteria have been met at screening. Investigators, in coordination with the medical officer, or delegate of the sponsor, 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 drug 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 of the following criteria to be enrolled in the trial.

1. Subject 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).
2. Subject must be at least 18 years of age.
3. Subject must have measurable disease as assessed by the investigator per RECIST v1.1.
4. Subject must have a life expectancy of >3 months.
5. Subject must qualify for palliative SBRT as an available option for disease management. Subjects will be eligible if the radiation therapy fraction specified in the protocol can be delivered safely per SOC.
6. For part 1 only: Subject must have histologically confirmed non-CNS solid tumor including CRC, NSCLC, SCLC, breast cancer, esophageal cancer, cervical cancer, anal cancer, pancreatic adenocarcinoma, prostate cancer, or HNSCC. The subject must have disease that is metastatic and for which there is no available systemic standard therapy likely to confer clinical benefit, or not be a candidate for such available therapy and for whom, in the opinion of the investigator, experimental therapy may be beneficial.
7. For part 2 only: Subject must have a histologically confirmed non-CNS solid tumor that is metastatic including NSCLC, CRC, breast cancer, and 1 to 3 of the tumors that had a signal of antitumor activity observed during the dose-finding part of this trial. Subjects must have received at least 1, but no more than 3, prior systemic treatment regimens including established SOC (maintenance treatment is considered part of 1 treatment line) for advanced/metastatic disease with documented PD on or after last prior treatment.

8. Criterion modified per Amendment 2

8.1 For both part 1 and 2:

For subjects with CRC, breast cancer, prostate cancer, and pancreatic cancer, where CPI is not approved as SOC: Subject has not received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or anti-CD40 agent, or with an agent directed to another stimulatory or co-inhibitory TCR (eg, CTLA-4, OX 40, 4-1BB).

For subjects with NSCLC, SCLC, TNBC, esophageal cancer, cervical cancer, anal cancer, or HNSCC:

- a) Subject is either ICI treatment naive OR
- b) Has been treated for at least 3¹ months with an approved anti-PD-1/PD-L1/anti-CTLA4 mAb administered either as monotherapy, or in combination with chemotherapy
- c) Has demonstrated a radiographic disease progression during or after the last dose of ICI treatment, if applicable.

For subjects with HNSCC of oropharynx and cervical cancer, documentation of tumor HPV status is required (eg, p16 IHC testing). Tests done on primary tumor specimens per local SOC are sufficient to meet this criterion.

9. Criterion modified per Amendment 2

9.1 Subjects must have at least 2 and no more than 6 separate extracranial lesions (including primary tumor if present), with each having a size of ≤ 5 cm. One lesion up to 10 cm in diameter is allowed if this lesion can be irradiated (all other lesions must have a size of ≤ 5 cm).

- a) At least 50% of lesions must be safely amenable to irradiation in the opinion of the treating radiation oncologist. This can be a lesion that was previously irradiated if prior radiation preceded projected first fraction of SBRT by at least 6 months.
- b) There is at least 1 measurable lesion (per RECIST 1.1 criteria) that can be spared from the RT field.
- c) A maximum of 3 metastases (of more than 1 cm) in any organ is allowed. However, the maximum allowed number of metastases is 6, of which no more than 3 metastases must be >1 cm. Other exceptions may be considered with sponsor consultation.

10. All subjects must be willing to provide newly obtained FFPE tumor tissue from core or excisional biopsies. Collections will be obtained from 1 lesion that will receive radiation and 1 that will not receive radiation during the course of the trial for biomarker research. Baseline biopsies can be fresh or from properly stored archival (<6 months old) samples where no other antitumor treatment has been administered between time of the biopsy collection and C1D1. A second on-treatment tumor biopsy will be collected from lesions that are deemed medically feasible after the second dose of GEN1042.

¹See Kluger, H. M., Tawbi, H. A., Ascierto, M. L., Bowden, M., Callahan, M. K., Cha, E., Chen, H. X., Drake, C. G., Feltquate, D. M., Ferris, R. L., *et al.* (2020). Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce. *J Immunother Cancer* 8.

11. Subject must have ECOG PS of 0 or 1 at screening, and confirmed on C1D1 prior to the administration of the first dose.

12. Subject must have adequate organ and bone marrow function as follows:

- a) Bone marrow/hematological function:
 - Absolute neutrophil count $\geq 1.5 \times 10^9/L$
 - Hemoglobin ≥ 9.0 g/dL
 - Platelet count $\geq 100 \times 10^9/L$
- b) Liver function:
 - Total bilirubin $\leq 1.5 \times \text{ULN}$ OR direct bilirubin $\leq \text{ULN}$ for subjects with total bilirubin levels $> 1.5 \times \text{ULN}$
 - ALT and AST $\leq 2.5 \times \text{ULN}$ or $\leq 5 \times \text{ULN}$ for subjects with liver metastases.
- c) Coagulation status:
 - PT/INR $\leq 1.5 \times \text{ULN}$ unless the subject is receiving anticoagulant therapy*
 - aPTT or PTT $\leq 1.5 \times \text{ULN}$ unless the subject is receiving anticoagulant therapy*

*Subjects receiving anticoagulant therapies should have the PT/INR or aPTT/PTT within the therapeutic range of intended use of anticoagulants (if applicable).

- d) Renal function:
 - Creatinine $\leq 1.5 \times \text{ULN}$ OR estimated GFR ≥ 45 mL/min/1.73 m² eg, according to the abbreviated MDRD equation:
$$\text{eGFR} = 186 \times (\text{SCr}^{-1.154}) \times (\text{age}^{-0.203})$$

where SCr, the serum creatinine level, is expressed in mg/dL; multiply it by 0.742 if the subject is female; multiply it by 1.212 if the subject is of African descent.

13. Criterion modified per Amendment 3

13.1 Sexually active men or WOCBP must agree to use a highly effective method of contraception supplemented with a barrier method, or to abstain from sexual activity during the trial, for at least 1 month after receiving the last dose of GEN1042, or for at least 4 months after receiving the last dose of pembrolizumab, if applicable. Reproductive potential and adequate contraception (ie, highly effective methods of contraception) are defined in [10.3](#).

Note: If the reproductive potential changes after start of the trial (eg, female subject who is not heterosexually active becomes active, female subject experiences menarche) a female subject must begin adequate contraception (ie, highly effective methods of contraception), as described in [10.3](#).

14. Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea or surgically sterile) must have a negative serum β -hCG pregnancy test result (within 7 days of C1D1) and a negative urine test within 24 hours prior to initiation of trial drug.

15. Criterion modified per Amendment 3

15.1 A female subject must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial and for at least 1 month after the last dose of GEN1042, or for at least 4 months after receiving the last dose of pembrolizumab.

16. Criterion modified per Amendment 3

16.1 Male subjects (including males who have had vasectomies) whose partner is pregnant should use condoms for the duration of the trial and for at least 1 month after the last dose of GEN1042, or at least 4 months after receiving the last dose of pembrolizumab.

17. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

18. Prior to the start of SBRT, subjects should have recovered from any clinically significant AEs (as deemed by the investigator), from their most recent therapy/intervention prior to enrollment.

5.2 Exclusion Criteria

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

1. Subject has a history of other prior malignancy, with the exception of non-melanoma skin cancers and in situ cancers such as the following: bladder, gastric, colon, cervical/dysplasia, melanoma, prostate, or breast, or has undergone potentially curative therapy with no evidence of disease recurrence for at least 3 years prior to the first trial treatment and no additional therapy is required or anticipated to be required during the trial period. Other exceptions may be considered with sponsor consultation.
2. Subject discontinued prior ICI treatment due to grade 3 or higher irAEs.
3. Subject has had palliative or curative RT within 14 days prior to SBRT.
4. Subject has any condition that is contraindicated to RT, such as connective tissue disorders with significant vasculitis (systemic lupus erythematosus or scleroderma), significant pre-existing lung disease if diffusing capacity is severely reduced in subjects requiring thoracic radiation, inflammatory bowel diseases in subjects where the gastrointestinal tract will receive RT, or presence of a pacemaker in the RT field.
5. Subject has a rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating investigator.
6. CNS is the only metastatic site or subject has known active or untreated CNS metastases and/or carcinomatous meningitis (regardless of clinical stability), or spinal cord compression.

Note: Subjects with previously diagnosed brain metastases may participate provided they are stable (without evidence of progression by imaging, using the identical imaging modality for each assessment, either MRI or CT scan, for at least 4 weeks prior to the first dose of trial

treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not used steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

7. Subject has an active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
8. Subject has a 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.
9. Subject has had an allogeneic tissue/solid organ transplant.
10. Subject has a history of (non-infectious) pneumonitis that has required oral or IV steroids or currently has pneumonitis that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
11. Subject has an active infection requiring systemic therapy.
12. Subject has contraindications to the use of pembrolizumab per local prescribing information.
13. Subject has received any treatment known to induce radiosensitization that finished within 5 elimination half-lives prior to the start of SBRT. Radiosensitizer treatments include (but are not limited to) chemotherapeutic agents (5-fluorouracil, gemcitabine, doxorubicin, docetaxel, vinorelbine, carboplatin, cisplatin, methotrexate, bleomycin, hydroxyurea), and radiation enhancement agents (eg, ErbB family receptor blockers, bevacizumab, any BRAF inhibitor, or MEK inhibitor), or any prior investigational agent with such clinically significant activity.
14. Criterion modified per Amendment 3
 - 14.1 Subject is a female who is pregnant, breast-feeding, or planning to become pregnant while enrolled in this trial or within 1 month after the last dose of GEN1042 or 4 months after the last dose of pembrolizumab.
15. Criterion modified per Amendment 3
 - 15.1 Subject is a male whose partner plans to have a child with this male subject while enrolled in this trial or within 1 month after the last dose of GEN1042 or 4 months after the last dose of pembrolizumab.
16. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol specified assessments.
17. Subject has a known history of HIV infection (HIV 1/2 antibodies).

18. Subject has a positive test for HBV (defined as positive for hepatitis B surface antigen or HBV DNA) or HCV (defined as positive for HCV antibody or HCV RNA) per local standard, indicating acute or chronic infection.
19. Subject has received prior treatment with a live, attenuated vaccine within 30 days prior to initiation of GEN1042 ± pembrolizumab. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines that are not allowed. Experimental and/or non-authorized SARS-CoV-2 vaccinations are not allowed.
20. Subject has a history of $\geq$ grade 3 anaphylaxis to mAb therapy as well as known or suspected allergy or intolerance to any agent given during the course of this trial.
21. In accordance with the French Public Health Code (Articles L1121-5 to L1121-8, and L1122-1-2), the following protected persons would not be considered for this trial:
 - a. Persons deprived of liberty
 - b. Adult persons under legal protection
 - c. Adult persons in emergency situation incapable of giving consent
 - d. Pregnant, parturient, and breastfeeding women
 - e. Minor persons
 - f. Persons admitted to a health or social institution for purposes other than research

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). Minimal information to be documented includes demography, reason for screening failure (eg, eligibility criteria not met, subject withdrew consent, or other reasons), and any SAEs or AEs related to a trial assessment.

Individuals who do not meet the criteria for participation in this trial (screen failures) may be rescreened once, with the exception of subjects who received SBRT and failed to start immunotherapy within 7 days. The rescreening must be approved by the sponsor to ensure that the safety of the subject is not compromised. All eligibility criteria must be re-assessed at the rescreening visit.

The following screening assessments may be used for rescreening if performed ≤ 35 days prior to C1D1 or if approved by the sponsor:

- CT and MRI scans with acquisition date prior to SBRT. Scans that exceed the screening window for the applicable cohort may be used for trial enrollment pending discussion and agreement between the investigator and the sponsor.

- Screening laboratory assessments with the protocol-defined timelines as indicated in Section [1.2](#).
- Previously submitted tumor biopsy sample.

Rescreened subjects are required to sign a new ICF if updates have been made since signing the most recent ICF.

6 TRIAL TREATMENT

6.1 Trial Treatment(s) and Therapy Administered

Trial treatment is defined as any IMP, AMP, or medical device(s) intended to be administered to a trial subject according to the trial protocol. IMP(s) specifically are referred to as trial drug(s). In this trial, both GEN1042 (unauthorised in EU) and pembrolizumab (authorised in EU) are considered IMP.

Trial treatment should be administered as described in [Table 4-2](#) until 1 or more of the discontinuation criteria in [Section 7](#) are met. Detailed dose modification guidance is provided in [Section 6.6](#). Information regarding concomitant therapy is provided in [Section 6.5.2](#). For additional guidance on trial treatment, refer to the IMP Manual.

6.1.1 *GEN1042 and Pembrolizumab*

GEN1042 and pembrolizumab are IMPs administered as IV infusions, by qualified site personnel. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

All subjects starting any part of the trial will first undergo SBRT. In part 1 (dose finding) of the trial the regimen will follow the dose and fractionation described in [Table 4-2](#). Subjects in cohort 1 will receive GEN1042 following completion of RT, as shown in [Figure 4-1](#). For cohort 2, GEN1042 infusion will be administered first followed by pembrolizumab. Based on convenience for the subject and institution, the gap between administration of GEN1042 and pembrolizumab can range from 30 min to 2 hours (meal breaks, short walks, managing IRRs, etc) as long as the start times of every component of combination regimen are duly recorded.

In both parts of the trial, treatment with GEN1042 ± pembrolizumab should start within 7 days after the last fraction of SBRT.

6.1.2 *Image-Guided, High-Dose Stereotactic Body Radiotherapy*

Image-guided, SBRT allows for the delivery of high-dose-per-fraction RT with exquisite precision while excluding to a large degree normal tissue from being exposed to high-dose regions of irradiation. SBRT is defined as the directing of therapy using beams of radiation along any trajectory in 3D space toward a target of known 3D coordinates. The coordinate system is defined by reliable fiducial markers and additional fiducials may be inserted whenever needed for tumor visualization. Image evaluation will be done prior to each session to confirm tumor locations and reduce set-up error and organ motion. For the purposes of this trial, the tumor itself will serve as the fiducial. The RT delivery systems that will be used in this trial are standard systems used for this type of treatment. Stereotactic delivery based on techniques such as Novalis or Cyberknife or equivalents may be used. The dose fractionation schemes in this trial have been used routinely at tertiary care centers.

SBRT will be delivered over 1 week before the start of systemic therapy with GEN1042 with or without pembrolizumab, using 6MV photons or other energies with standard field encompassing

tumor. At least 50% of tumor lesions will receive radiation and the remaining tumor site(s) will not be radiated in order to properly assess the potential abscopal effect.

Treatment at the protocol-specified radiation dosing regimen is permitted only if the normal tissue criteria are met. If the normal tissue criteria cannot be met at the radiation therapy fraction specified in the protocol, the subject is not eligible for enrollment.

Tumor size will be ≤ 5 cm according to recent imaging (CT, MRI, or PET/CT). One lesion up to 10 cm is allowed if this lesion can be irradiated. Lesions larger than 5 cm may be treatable depending on location and with careful attention to dose constraints ([Lievens et al., 2020](#)). The radiation dose will be prescribed to the 90% isodose line in order to deliver 95% of the planned dose to 95% of the planned tumor volume. The dose used to treat a given metastasis will be based on the location of the metastasis, as normal tissue toxicity is likely to arise from the organs at risk surrounding the metastasis.

If there are lesions only in the liver, at least 1 lesion needs to be spared from irradiation for the abscopal response assessment. Otherwise, the largest lesion(s) should be irradiated, if possible.

Subjects will be eligible if dose constraints to organ at risk are respected (for SBRT dose constraints please see ([Pollom et al., 2017](#))).

The RT software tools, and accurate dose calculations allow for better targeting of tumors, while providing motion management for precise dose delivery. Generally, this technique includes:

- 4D CT data integration for moving target such as lung tumors
- Subject's immobilization with a vacuum cushion
- Precise type B dose calculation algorithm (Monte Carlo, or other type B dose calculation algorithms)
- Monitoring of respiratory motion
- Real-time detection and compensation of tumor motion (on-board CT)

The definition of volumes will be in accordance with the International Commission on Radiation Units and Measurements Reports #50, #62, and #83.

RT will be given on alternate days for the 3×9 Gy scheme and only type B dose calculation algorithms will be accepted. For the 5×5 Gy scheme, RT will be given on consecutive weekdays (Monday to Friday). SBRT regimen is expected to be completed within 7 days. In order to account for weekends, public holidays etc., a 3-day window is allowed to complete the planned SBRT scheme.

Margins from GTV (or ITV) to PTV are of 5 - 10 mm to account for set-up error and organ motion.

Any organ that is traversed by part or all of a beam should be contoured so that the dose it receives can be assessed. Organs should be outlined by the treating radiotherapist (or dosimetrist

and checked by treating radiotherapist). Dose constraints are adapted to the standard recommendations (Pollom et al., 2017).

6.1.3 GEN1042 Monotherapy

GEN1042 will be administered as a fixed-dose IV infusion on Day 1 of each 3-week treatment cycle (21 days) after all pre-treatment procedures and assessments have been completed, and SBRT treatment has finished. The duration of each IV infusion will depend on the dosage assigned; an infusion speed of up to 350 mg/hour is recommended. In the dose finding part, subjects will be administered GEN1042 according to dose levels outlined in Table 4-2. In the randomized part, subjects will be administered the RP2D of GEN1042 identified in the dose finding part. CCI

As a routine precaution, subjects dosed with GEN1042 must be monitored during the infusion and treated in an area with resuscitation equipment and emergency agents. The institutional standard for the observation period needed for monitoring IRRs should be followed. In the ongoing GCT1042-01 trial, no subjects have experienced an anaphylactic reaction. One subject experienced an IRR of grade 1 headache that resolved on the same day.

Subjects should be carefully monitored for IRRs. If an acute IRR is noted, subjects should be managed according to Section 6.6.

Refer to the administration (including duration of infusion) and preparation guidelines in the IMP Manual for additional information regarding GEN1042 administration.

6.1.4 GEN1042 Plus Pembrolizumab

After all pre-treatment procedures and assessments have been completed, and SBRT has finished, GEN1042 will be administered first followed by pembrolizumab infusion. Pembrolizumab 200 mg will be administered using a standard 30-minute IV infusion on Day 1 of each 3-week treatment cycle.

If pembrolizumab is sourced locally, please refer to the local prescribing information for more details on administration, storage, and handling.

Based on convenience for the subject and institution, the gap between administration of GEN1042 and pembrolizumab can range from 30 min to 2 hours (meal breaks, short walks, managing IRRs, etc) as long as the start times of every component of the combination regimen are duly recorded.

6.1.4.1 Physical Description

GEN1042 – formulated in CCI – is a clear to opalescent, colorless to slightly yellow solution supplied as a concentrate for solution for infusion to be diluted (at site) in 0.9% NaCl (saline).

Refer to the IB for a list of excipients.

6.1.4.2 *Packaging*

The trial drug will be provided in a 20R glass vial containing 10 mL of GEN1042 (100 mg/vial).

6.1.5 *Pembrolizumab*

6.1.5.1 *Physical Description*

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

6.1.5.2 *Packaging and Labelling*

Pembrolizumab labels will contain information to meet the applicable regulatory requirements. For further details regarding pembrolizumab packaging and labeling, refer to the IMP manual.

6.1.6 *Complaint Handling*

A 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.

6.1.6.1 *Procedures*

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

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

6.1.6.2 *Contacting Sponsor Regarding Complaints*

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding complaint issues are listed on the sponsor Contact Information page, which will be provided separately from the protocol.

6.2 *Preparation/Handling/Storage/Accountability*

6.2.1 *Preparation, Handling, and Storage*

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

6.2.2 *Drug Accountability and Destruction*

The investigator or designee must maintain an accurate record of received, returned, and/or destroyed IMP 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 unused trial IMP (vials, capsules, pre-filled 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 made at the end of the trial in accordance with local regulations and guidelines (Note, it is advisable that site monitors confirm accountability of IMP batches supplied by Genmab upon batch expiry).

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 *Subject Numbering*

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

6.3.2 *Treatment Assignment/Randomization*

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

In part 1, subjects will be allocated to the appropriate dose of GEN1042 based on the dose level assigned.

In part 2, provided both GEN1042 alone and in combination with pembrolizumab are deemed safe following SBRT, randomization will be used to avoid bias in the assignment of subjects to treatment arms, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms.

On the day before C1D1, subjects will be assigned to 1 of 2 treatment arms based on a computer-generated randomization schedule prepared by the sponsor before the trial. The randomization will be balanced using randomly permuted blocks and will be stratified by prior CPI treatment (yes vs no) and number of lesions (≤ 3 , > 3).

In the scenario in which GEN1042 cannot be safely combined with pembrolizumab, part 2 will be a single arm trial.

6.4 Compliance

The trial treatments will be administered in the controlled environment of a clinical research center, and the direct observation of trial treatment administration by trial staff will ensure compliance with trial requirements. The date and time of each trial treatment administration will be documented.

6.5 Prior Therapies and Concomitant Medications

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

6.5.1 Prior Anticancer Therapies

Prior anticancer therapies (including surgery, RT, chemo-radiotherapy, and systemic treatment regimens) for the indications under study are defined as any anticancer therapies received after initial diagnosis but prior to the first infusion of GEN1042 ± pembrolizumab on C1D1. If the subject had a prior investigational agent likely to significantly interact with the IMP based on its MoA, there must be a washout period and the agent stopped 5 elimination half-lives before administration of the first infusion. The start and stop dates of anticancer treatment, best response, reason for the treatment and discontinuation, and date of progression should be reported for prior anticancer therapies.

Refer to Section [6.5.2.2](#) for details regarding prohibited prior anticancer therapies or washout periods for prior anticancer therapies.

6.5.2 Concomitant Medications

Concomitant medications are defined as therapies (including over-the-counter or prescription medications, vitamins, and vaccines) started either prior to or on the same day as the first infusion of GEN1042 ± pembrolizumab on C1D1 and continued throughout the trial. The subject must be told to notify the investigational site about any new medications (including over-the-counter or prescription medicines, vitamins, and vaccines) he or she takes.

All medications (other than the trial treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications, and blood transfusions) administered within 28 days prior to C1D1, during the trial, and up to 30 days after the last dose of GEN1042/pembrolizumab must be recorded in the eCRF.

Information recorded in the eCRF should contain the following information:

- Start date
- Medication name, route of administration, and frequency
- Stop date of administration or ongoing at trial termination
- Indication/reason for use
- The total daily dose should be filled in whenever possible

All concomitant medications 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.

All concomitant medications administered during AEs or SAEs are to be recorded.

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as “prohibited” (Section 6.5.2.2).

6.5.2.1 *Permitted Concomitant Medications and Therapies*

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

- 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. SARS-CoV-2 vaccine should not be administered during the DLT observation period.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia and $\geq$ grade 3 neutropenia, when clinically indicated or at the investigator’s discretion. In case of recurring $\geq$ grade 3 neutropenia, use of growth factors is mandated.
- Red blood cell and platelet transfusions, if clinically indicated.
- Multivitamins, vitamin D, calcium, and supplements, for prevention of weight loss.
- Prescribed medicinal cannabinoids as palliative therapy.
- Steroid treatment is permitted to modulate symptoms of an irAE at the discretion of the investigator (refer to Section 6.6.3). Replacement therapy (eg, thyroxine, insulin), or corticosteroid replacement therapy for adrenal or pituitary insufficiency is allowed. Anticonvulsants used in subjects with brain metastases/primary cancer who have experienced seizures are also allowed.
- Bisphosphonates (eg, pamidronate, zoledronic acid, etc) and denosumab.

6.5.2.2 *Prohibited Concomitant Medications*

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

Known prior medications that exclude a subject from participating in the trial are described in the exclusion criteria (Section 5.2). The following medications and substances are prohibited during the trial (unless utilized to treat a drug-related AE):

- Any concurrent anti-neoplastic therapy (eg, chemotherapy, hormonal therapy, immunotherapy not specified in this protocol, radiation therapy, or standard or investigational agents not defined in the protocol)
 - Note: Palliative radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator’s discretion. If the radiation therapy happens before the first CT scan (on Week 6 $\pm$ 7 days), the subject should be replaced (though subject may continue in the trial).

- Immunosuppressive agents
- 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, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).
- Live or live attenuated vaccines within 30 days prior to the first dose of trial treatment, while participating in the trial, and for 3 months following the last dose of GEN1042/pembrolizumab.

Note: Seasonal influenza vaccines are generally killed virus vaccines and are permitted; however, intranasal influenza vaccines are live attenuated and are not allowed.

Caution should be used regarding the use of herbal medications as there may be as yet unknown interactions with trial treatment. Discontinuation of the use of herbal medications prior to trial enrollment is encouraged.

For subjects receiving combination therapy with pembrolizumab, investigators should refer to the local product labelling for additional prohibited and restricted concomitant medications.

6.5.3 *Rescue Medicine*

Rescue medication to reverse the action of GEN1042 is not known (see Section 8.5 for treatment of overdose).

6.6 Dose Modifications and Dose Delay

Hold of Radiation Therapy

In general, radiation therapy will be held for grade 3 or higher radiation therapy-related, nonhematologic toxicity. Radiation therapy will resume at the discretion of the investigator at full dose when toxicity returns to grade 1 or 0. In addition, though development of symptomatic pneumonitis during the actual period of radiation treatment is unlikely, radiation therapy for any subject experiencing pneumonitis prior to completing the treatment should be put on hold until symptoms resolve and the case is clinically evaluated.

6.6.1 *Maximum Tolerated Dose and Dose-Limiting Toxicity*

The MTD is defined as the highest dose of GEN1042 studied alone or in combination with pembrolizumab for which the incidence of DLT is no more than 17% (ie, 1/6 subjects). AEs meeting DLT criteria experienced after the DLT observation period will be examined separately. The MAD will be recorded if the MTD is not reached.

The decision on changes in dose level or regimen during the dose-finding part will be mainly based on the DLTs observed during the DLT observation period.

A subject is considered DLT evaluable if he/she has received the treatment in cycle 1, has finished the DLT observation period (ie, 1 cycle of 21 days), and does not need to be replaced. Subjects who come off trial treatment for reasons other than DLT, including those with CTCAE

grade ≥ 3 allergic reaction/hypersensitivity to the trial drug(s) within the DLT window will be replaced.

The occurrence of any of the following toxicities will be considered a DLT, if judged by the investigator to be possibly, probably, or definitely related to GEN1042 monotherapy or combination regimen with pembrolizumab using CTCAE v5.0:

1. Grade 5 toxicity
2. Any treatment-related toxicity that causes the subject to discontinue treatment during cycle 1
3. **Hematological DLTs:**
 - Febrile neutropenia grade 3 or grade 4
 - Grade 3 thrombocytopenia associated with clinically significant bleeding
 - Grade 4 thrombocytopenia of any duration
 - Grade 4 anemia
4. **Non-hematological Clinical DLTs:**
 - Any grade ≥ 3 non-hematologic clinical (non-laboratory) toxicity excluding:
 - a) Grade 3 electrolyte abnormality that lasts <72 hours, is not clinically complicated, and resolves spontaneously or responds to appropriate medical intervention per SOC
 - b) Grade 3 increase in amylase and/or lipase that is not associated with symptoms or clinical signs of pancreatitis or abnormalities on abdominal imaging
 - c) Grade 3 endocrinopathy that is well controlled by hormone replacement
 - d) Grade 3 rash meeting the following criteria: 1) improves to grade 1 within 2 weeks; 2) does not limit self-care; and 3) is not associated with infection
 - e) Grade 3 IRR that resolves to $\leq$ grade 1 within 24 hours
 - f) Grade 3 nausea or vomiting that lasts <48 hours, and resolves to $\leq$ grade 1 either spontaneously or with the use of anti-emetics per SOC
 - g) Grade 3 diarrhea that lasts <72 hours, does not result in hospitalization and resolves to $\leq$ grade 1 either spontaneously or with anti-diarrheal per SOC
 - h) Grade 3 fatigue for less than 7 days
5. **Any grade 3 or grade 4 non-hematologic laboratory value if:**
 - Clinically significant medical intervention is required to treat the subject or
 - The abnormality leads to hospitalization, or
 - The abnormality persists for >7 days.
 - The abnormality results in a DILI as defined by Hy's Law below:
 - a) Aminotransferase (ALT and/or AST) >3 x ULN; and
 - b) Total bilirubin >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase); and

- c) No other reason can be found to explain the combination of increased ALT/AST and total bilirubin
- Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc

Note: Due to the potential overlap of AEs (eg, hematological AEs) between SBRT and immunotherapies, toxicity during the DLT observation period could be attributable to SBRT. Hematological AEs, if recovered to grade ≤ 1 within 7 days with or without treatment following SOC or institutional standard, should not be considered a DLT. Toxicities that are clearly associated with RT alone and/or that have a clear-cut alternative explanation should not be deemed as DLT.

The investigator must notify the medical monitor immediately of a DLT. Frequent laboratory monitoring should be initiated to document start and resolution of relevant (eg, hematological, hepatic) AEs.

For selection of the RP2D in the randomized part and for further development, the totality of the available data, including safety, antitumor activity, PK, and biomarkers will all be taken into consideration.

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.

6.6.2 *Dose Modification Guidance and Stopping Criteria*

NCI-CTCAE v5.0 will be used to grade the intensity of AEs.

Radiation related toxicity will be managed per SOC and/or institutional standard.

6.6.2.1 *Dose Modification for GEN1042*

No intra-subject dose modification (increase or decrease) of GEN1042 will be permitted for this trial; however, the dose of GEN1042 may be delayed.

Note that specific rules apply for elevated liver parameters, irAEs, and IRRs (see Section 6.6.3).

- Administration of GEN1042 can be delayed for up to 42 days (ie, 2 cycles) unless otherwise approved by the sponsor medical monitor. If the intensity resolves to $\leq$ grade 1 or baseline within this period, re-treatment may be considered under the following:
 - Sponsor and investigator will discuss any safety concerns in order to decide whether the dosing interval in subsequent cycles should be adjusted by 1-3 weeks (eg, to 4-5 weeks).

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

For CRS occurring during GEN1042 or GEN1042 + pembrolizumab administration, the CRS grading should follow ASTCT criteria (Lee et al., 2019). Please refer to 10.7 and 10.8 for CRS grading and management guidelines.

6.6.3 Dose Modification for Specific Adverse Events

6.6.3.1 Immune-Related AEs Associated with Pembrolizumab and/or GEN1042

AEs associated with GEN1042, or GEN1042 and pembrolizumab combination exposure, may represent an irAE. These irAEs may occur shortly after the first dose or several months after the last dose of study treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of study treatment, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with GEN1042 ± pembrolizumab are provided in Table 6-1 (see also (Schneider et al., 2021)).

Attribution of Toxicity

When trial interventions are administered in combination, attribution of an AE to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to GEN1042 alone, or to pembrolizumab alone, AEs listed in both interventions must be held according to the criteria in Table 6-1. In cohorts when only GEN1042 is administered, the expectation is to assess relatedness to the administered therapy.

Holding Trial Interventions

When pembrolizumab/GEN1042 are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications. In cohorts where GEN1042 is administered as monotherapy, potential dose delay or discontinuation should follow respective guidance (Section 6.6.2.1 and Section 7).

Restarting Trial Interventions

If the toxicity does not resolve or the criteria for resuming treatment are not met, the subject must be discontinued from all trial interventions. If the toxicities do resolve and conditions are aligned with what is defined in Table 6-1, the combination of GEN1042 and pembrolizumab or GEN1042 monotherapy may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to GEN1042 alone, the treatment should be permanently discontinued if not tolerated. Subjects may continue to take pembrolizumab outside of the trial if appropriate.

Table 6-1 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with GEN1042 ± Pembrolizumab

<p>General instructions:</p> <ol style="list-style-type: none"> 1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab/GEN1042 must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last study drug administration. 3. The corticosteroid taper should begin when the irAE is $\leq$ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab/GEN1042 has been withheld, pembrolizumab/GEN1042 may resume after the irAE decreased to $\leq$ Grade 1 after corticosteroid taper. 				
irAEs	Toxicity Grade (CTCAE v5.0)	Action with Pembrolizumab/ GEN1042	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Thrombocytopenia	Grade 2 or 3	Withhold	Administer prednisone 1 mg/kg/d orally for 2-4 weeks after which time medication should be tapered over 4-6 weeks to the lowest effective dose. IVIG may be used in conjunction with corticosteroids if a more-rapid increase in platelet count is required.	Monitor for improvement; if not resolved, withhold pembrolizumab/GEN1042 until AE has reverted to Grade 1
	Grade 4	Withhold or permanently discontinue	Administer prednisone 1 to 2 mg/kg/d (oral or IV depending on symptoms).	If worsening or no improvement, administer 1-2 mg/kg/d prednisone equivalents and permanently discontinue pembrolizumab/GEN1042

irAEs	Toxicity Grade (CTCAE v5.0)	Action with Pembrolizumab/ GEN1042	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
			<p>IVIG should be used with corticosteroids when a more-rapid increase in platelet count is required. If IVIG is used, the dose should initially be 1 g/kg as a 1-time dose. This dosage may be repeated if necessary.</p> <p>If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression.</p>	
Diarrhea/colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	<p>Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood, or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus)</p> <p>Subjects with $\geq$ grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis</p> <p>Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion</p>
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action with Pembrolizumab/ GEN1042	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT elevation or increased bilirubin	AST/ALT >3.0 to 5.0 x ULN if baseline normal and bilirubin <2 x ULN or >3.0 to 5.0 x baseline if baseline abnormal and bilirubin <2 x baseline if baseline abnormal	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper.	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	AST/ALT >5.0 to 10.0 x ULN if baseline normal and total bilirubin <2 x ULN or >2.0 to 5.0 x baseline if baseline abnormal and total bilirubin: <2 x baseline if baseline abnormal	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. If the abnormality improves to grade 1, the dose of corticosteroids can be tapered over 4 weeks. If LFTs return to baseline values within 1-2 weeks, therapy may be resumed with close monitoring of hepatic biochemical tests once the dose of corticosteroid reaches 10 mg/day.	
	AST/ALT >10.0 to 20.0 x ULN if baseline normal and total bilirubin <2 x ULN or AST/ALT >5 x baseline if baseline abnormal and total bilirubin <2 x baseline if baseline abnormal	Withhold		

irAEs	Toxicity Grade (CTCAE v5.0)	Action with Pembrolizumab/ GEN1042	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
	AST/ALT >5.0 to 20.0 × ULN if baseline normal and total bilirubin >2 × ULN or >5 × baseline if baseline abnormal and total bilirubin >2 × baseline if baseline abnormal	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper.	
	Grade 4	Permanently discontinue		
Hepatitis with no tumor involvement of the liver	AST or ALT increase >3 to 8 × ULN OR Total bilirubin increases to >1.5 to 3 × ULN	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	AST or ALT increase to >8 × ULN OR Total bilirubin increases to >3 × ULN	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

irAEs	Toxicity Grade (CTCAE v5.0)	Action with Pembrolizumab/ GEN1042	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hepatitis with tumor involvement of the liver ^a	Baseline AST or ALT is >1 and up to 3 × ULN and increases to >5 and up to 10 × ULN OR Baseline AST or ALT is >3 and up to 5 × ULN and increases to >8 and up to 10 × ULN	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	ALT or AST increases to >10 × ULN OR Total bilirubin increases to >3 × ULN	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for subjects with T1DM Administer antihyperglycemic in subjects with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue ^b		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue ^b		

irAEs	Toxicity Grade (CTCAE v5.0)	Action with Pembrolizumab/ GEN1042	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3, or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3, or 4	Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	Persistent grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event ^c		
	Recurrent grade 3 or grade 4	Permanently discontinue		

Note: Non-irAEs will be managed as appropriate, following clinical practice recommendations.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Reaction with Eosinophilia and Systemic Symptom; GI=gastrointestinal; ir=immune-related; IV=intravenous(ly); IVIG=intravenous immunoglobulin; LFT=liver function test; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

a. If AST and ALT are ≤ ULN at baseline, withhold or permanently discontinue GEN1042/pembrolizumab based on recommendations for hepatitis with no liver involvement.

b. The decision to withhold or permanently discontinue GEN1042/pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ grade 2, GEN1042/pembrolizumab may be resumed.

c. Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

For additional guidance on the recommended management of irAEs, please refer to the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Practice Guideline ([Schneider et al., 2021](#)).

6.6.3.2 *Infusion-Related Reactions Associated with GEN1042 Monotherapy*

The following treatment guidelines are provided below for subjects who experience an IRR associated with administration of GEN1042 monotherapy.

- Grade 1: If an IRR grade 1 occurs, the infusion does not need to be interrupted and can be continued at the investigator's discretion at half the infusion rate under close medical supervision.
- Grade 2-3: If an IRR grade 2 or 3 occurs, the infusion should be interrupted, and appropriate medical management instituted. The infusion may be re-started at the investigator's discretion at half the infusion rate under close medical supervision if symptoms have resolved to $\leq$ grade 1 within an hour.
 - Subjects who have experienced prior infusion-related grade 2 or 3 reactions in the trial should be pre-medicated. Pre-medication 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 pre-medication, the infusion should be stopped, and the subject should be withdrawn from GEN1042 monotherapy.
- Grade 4: If anaphylaxis or grade 4 IRR occurs, administration of GEN1042 should be discontinued immediately and permanently and appropriate medical therapy should be administered.

Note:

- As a routine precaution, subjects dosed with GEN1042 must be monitored during the infusion and treated in an area with resuscitation equipment and emergency agents. All subjects must be observed for 1 hour after ending the first infusion of GEN1042. After the first infusion, the 1-hour observation window is not required unless clinically indicated.
- At all times during GEN1042 infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, for instance, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.
- All pre-medication must be reported on the concomitant medication page in the eCRF.

6.6.3.3 *Infusion-Related Reactions Associated with Pembrolizumab*

For the management of pembrolizumab related IRRs, please follow the institutional standard or local prescribing information.

6.7 Treatment after the End of the Trial

6.7.1 *Subject Contact and Trial Treatment After the End of the Trial*

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

7 DISCONTINUATION OF TRIAL TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Treatment

Discontinuation of trial treatment (all trial components) does not represent withdrawal from the trial. For subjects in the combination arm, if a subject discontinues GEN1042, pembrolizumab must also be discontinued. Subjects should continue to be monitored according to the applicable schedule outlined in Section 1.2; however, subjects must be discontinued from trial treatment if 1 of the following criteria is met:

- Radiographic PD or confirmed radiographic PD by iRECIST (if applicable)

Note: Subjects may continue treatment with GEN1042 ± pembrolizumab beyond RECIST 1.1 progression if they had investigator-assessed clinical benefit, no rapid disease progression, tolerance to trial treatment, stable ECOG PS, and continuing treatment would not delay any intervention to prevent serious complications of disease progression. GEN1042 should be permanently discontinued in the case of a dose delay of more than 42 days due to toxicity possibly related to GEN1042, unless otherwise approved by the sponsor medical monitor.

- Any palliative surgery that involves tumor lesions
- Clinical progression
- Unacceptable AE requiring treatment discontinuation. This includes an irAE (refer to Section 6.6.3.1) or IRR (refer to Section 6.6.3.2) of grade ≥ 3 .
- Investigator believes it is in the best interest of the subject to stop treatment
- Subject requests to stop trial treatment (but not withdrawal of consent for the trial)
- Subject non-compliance
- Pregnancy
- Termination of the trial by the sponsor (Genmab)
- Completion of 35 administrations (approximately 2 years) of pembrolizumab (for subjects in combination therapy cohorts only) (GEN1042 may be continued if pembrolizumab is discontinued)

Note: The number of administrations is calculated starting with the first dose of pembrolizumab.

In addition, discontinuation of treatment may be considered for subjects who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks).

If GEN1042 treatment is permanently discontinued for other reasons than radiographic PD, every effort should be made to continue tumor assessments. In addition, the treatment

discontinuation, safety follow-up and survival follow-up should continue as specified in the Schedule of Activities (see Section 1.2).

To the greatest extent possible, subjects should be examined as soon as possible, and the treatment discontinuation visit should be performed, irrespective of the reason for discontinuation. If the treatment discontinuation evaluations coincide with a regularly scheduled cycle visit, the treatment discontinuation evaluations will supersede those of the regularly scheduled cycle visit.

After treatment discontinuation, the subject should receive suitable treatment as decided by the investigator (see Section 6.7).

7.2 Withdrawal from the Trial

Subjects are to be withdrawn from the trial (Part 1 or Part 2) for the following reasons:

- A subject may withdraw consent from the trial at any time at his or her own request
- Sponsor or investigator decision
- Lost to follow-up (see Section 7.5)
- Death
- Trial closure

When a subject withdraws before completing the trial, the reason for withdrawal is to be documented. If a subject discontinues trial treatment and withdraws from the trial before demonstrating PD, the end-of-treatment assessments should be obtained. 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 consent. If a subject withdraws from the trial, he or she may request destruction of any samples taken and not analyzed, and the investigator must document this in the site trial records.

The investigator and sponsor will make every effort to ensure subject data are followed for completion of all trial safety assessments (see Section 1.2) at the time of trial discontinuation.

7.3 Withdrawal from the Use of Research Samples

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

7.4 Safety Follow-up Evaluation

Subjects discontinuing from treatment for any reason will have a post-treatment safety follow-up visit 30 days (+7 days) after the subject receives the last dose of trial drug. If the subject initiates new anticancer treatment within 30 days of the last dose of trial drug, 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 8.2.5).

For subjects receiving the pembrolizumab-containing regimen, a safety post-treatment follow-up visit occurring 90 days (± 7 days) after the subject receives the last dose should be done if trial drug-related toxicity persists.

7.5 Lost to Follow-up

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

7.6 Withdrawal of Consent

Subjects who request to discontinue trial drug will remain in the trial and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with trial drug only or also from trial procedures and/or post-treatment trial follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

8 TRIAL ASSESSMENTS AND PROCEDURES

The Schedule of Activities (Section 1.2) summarizes the frequency and timing of assessments applicable to this trial.

Blood collections for PK and pharmacodynamic assessments should be kept as close to the specified time as possible.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, 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 conducted under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

8.1 Demography and Baseline Assessments

8.1.1 *Demographics*

The following demographic details will be assessed at screening:

Year of birth and/or age, race, ethnic origin, sex, smoking and drinking habits

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:

- Primary tumor site and staging (AJCC 8th edition) at diagnosis and at screening, including ECOG PS ([Amin et al., 2017](#))
- Prior cancer treatment including systemic treatments, radiation, and/or surgeries
- Cytogenetics and molecular mutational status and protein expression levels relevant for tumor type, in particular:

NSCLC: the subject's tumor status with respect to EGFR mutations, and ALK, NTRK and RET rearrangement, BRAF, HER2, MET exon 14 mutations as per local assessment, PD-L1, expression as per local and/or central testing

SCLC: tumor PD-L1 IHC CPS as per local assessment

Cervical cancer: tumor PD-L1 IHC CPS as per local assessment, HPV p16 testing as per local standard testing

Esophageal cancer: tumor PD-L1 IHC CPS as per local assessment, tumor HER2 score by IHC or *HER2* amplification by ISH, as per local assessment

CRC: *KRAS* mutational status; MSI status; MMR status; *BRAF V600E* mutation status

HNSCC: tumor PD-L1 IHC CPS as per local assessment, HPV p16 testing as per local SOC

Breast cancer: HER2 status, *BRCA1/2*, hormone receptor status

PDAC: actionable mutations (such as *BRCA1/2* or *PALB2* mutations)

Additionally, if known, locally assessed cancer-associated mutations, gene signatures, tumor markers (eg, CA19-9 for PDAC, LDH for SCLC), and immune therapy prognostic targets for the listed above cancers or other non-CNS solid tumors considered for this trial may also be recorded (including but not limited to p53, HER2, BCL2, *RB1*, MSI status and/or PD-L1 expression, CA19-9, CEA, and SAA).

8.1.3 Medical History

Any medical condition (signs, symptoms, and diagnosis) occurring prior to the first dose of SBRT should be documented in the source documents as medical history.

Medical conditions that occur after the ICF is signed and prior to the first infusion should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (eg, SBRT, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications.

Any medical history/current medical condition that worsens after the first fraction of SBRT will be documented as an AE. See additional reporting details in Section 8.4 and 10.2.

8.2 Efficacy Assessments

8.2.1 Definition of Target and Non-target Disease

Standard definitions as per RECIST 1.1 criteria will be used throughout. Subject must have at least 2 and no more than 6 separate extracranial lesions, including primary tumor, with a size of ≤ 5 cm (one lesion up to 10 cm in diameter is allowed if this lesion can be irradiated [all other lesions must have a size of ≤ 5 cm]), of which at least half is amenable for irradiation. Trial specific assessments are to be done and evaluated locally.

8.2.2 Definition of Abscopal Response

An abscopal response describes RT-induced immune-mediated tumor regression at sites distant to the irradiated field. For the purpose of this trial, an abscopal response is defined as a reduction of at least 30% in diameter of the best responding unirradiated target lesion.

8.2.3 Assessment of Disease

Tumor response will be assessed locally according to the RECIST v1.1 criteria ([Eisenhauer et al., 2009](#)). Conventional imaging (CT/MRI scan) as per protocol must be used for RECIST 1.1 assessment. If other imaging modalities are used, such as PET/CT, then the measurements must be based on the CT portion with similar diagnostic quality to CT alone. Small lymph node lesions that are visible in eg, FDG-PET will only be considered a lesion if >1 cm in the short axis

according to a diagnostic CT measurement. Lymph nodes <10 mm are regarded as normal. Lymph nodes 10 to 14 mm are regarded as pathologic and can be used as non-target lesions. Lymph nodes with a short axis of ≥ 15 mm are considered measurable and assessed as target lesions.

Efficacy will be assessed by on-trial imaging as shown in the Schedule of Activities (see Section 1.2) until disease progression is assessed by the investigator, death, lost to follow-up, the start of new anticancer therapy, or withdrawal of consent, whichever occurs first.

Imaging assessments will be performed at screening/baseline prior to SBRT. Screening biopsies should be performed after imaging and prior to SBRT. All sites of metastatic disease are to be reported as target or non-target lesions at baseline and followed throughout the trial.

On-trial imaging should be performed from the date of first dose, every 6 weeks (± 7 days) until Week 48, and every 12 weeks (± 7 days) thereafter from the C1D1 visit until disease progression is assessed by the investigator, or until death, lost to follow-up, the start of new anticancer therapy, or withdrawal of consent, whichever occurs first. The first on-treatment imaging assessment and on-treatment biopsy must be done between C2D15 and C3D1 where it is considered feasible without a risk of complications. The imaging assessment must be prior to the biopsy. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts.

All scheduled tumor imaging, including at screening, must include complete imaging of the chest, abdomen, and pelvis. Tumor imaging is strongly preferred to be acquired by CT with iodinated contrast. For the abdomen and pelvis, MRI may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. Chest imaging must be done by CT, but may be done without contrast when iodinated contrast is contraindicated. Note: All on-trial imaging for HNSCC subjects should include the complete imaging of head, neck, chest, and abdomen. A CT from the vertex of the head to the thoracic inlet or a brain CT is strongly preferred. Imaging of the pelvis is optional.

All subjects with a history or a suspicion of brain metastasis should have an MRI of the brain (or CT with contrast if MRI is contraindicated) at baseline. A recent brain scan may be used for subjects who are asymptomatic, provided the scan was done within 35 days of C1D1 and prior to the first SBRT. MRI scans during on trial treatment and follow-up periods are required only if there is a prior history of lesions known at screening, or as clinically indicated for new signs and symptoms that suggest CNS involvement. The surveillance brain MRI should be performed approximately every 12 weeks, or sooner if clinically indicated.

If skin lesions are present at screening, color photography should be acquired using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.

Any potentially measurable lesion that has been previously treated with RT should be considered as a non-measurable lesion. However, if a lesion previously treated with RT has clearly progressed since the RT, it can be considered as a measurable lesion.

Chest X-rays and ultrasound should not be used to measure tumor lesions.

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 disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Up to 6 target lesions (including primary tumor; maximum 3 per organ) will be defined at screening and these must be followed throughout the trial. A lesion from which a biopsy has been taken during the trial cannot be a target lesion. At the discretion of the investigator, in subjects with 2 lesions, the target lesion/lesions can be biopsied if feasible during the trial with a time window of 4 weeks prior to the next imaging assessment. Non-target lesions will also be assessed throughout the trial. Initial tumor imaging at screening must be performed within 35 days prior to C1D1 and prior to SBRT. If a CT scan or MRI has been performed within 35 days prior to C1D1 as part of standard procedure, it is acceptable as a screening scan for the trial as long as it meets trial requirement. Scans that exceed the 35-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.

Localized CT with contrast or MRI (with or without contrast;) must be acquired for assessment of lesions of the skeleton/extremities if not visible on other images. At the discretion of the investigator, 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, and the use of contrast should be used throughout the trial to optimize the reproducibility of the assessment and preserve the accuracy of the assessment of response or progression.

The reading of the scans will be done by a local radiologist and/or investigator. Images will also be sent to a central location for anonymization and additional exploratory research evaluations. To the greatest extent possible, sites should maintain the same imaging reader 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.

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.

Images obtained at an unscheduled timepoint that determine PD should be captured in the eCRF.

8.2.3.1 Collection of Imaging

Tumor assessments for each subject should be submitted to the radiology vendor as they are performed on an ongoing basis.

8.2.4 *iRECIST Assessment of Disease*

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

iRECIST PD should be confirmed within 4-7 weeks after the first radiologic evidence of PD per RECIST 1.1 in clinically stable subjects. Subjects who have unconfirmed PD may continue on-trial treatment until progression is confirmed as long as the subject is clinically stable. Subjects who are clinically stable must meet the following criteria:

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

If repeat imaging shows iCPD, subjects will discontinue trial drug. However, if the subject is deriving benefit after iCPD is observed, an exception to continue trial drug must be approved by the sponsor medical monitor. If repeat imaging shows iSD, iPR, or iCR, imaging should be continued every 6 weeks (± 7 days) until Week 48, and every 12 weeks (± 7 days) thereafter from the C1D1 visit, and the subject should continue on trial drug. Subjects who have repeat imaging to confirm progression do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later.

8.2.5 *Survival Status*

Survival status will be assessed every 12 weeks (± 14 days) from the first dose for up to 2 years, or until the subject's death, whichever occurs first. The subject may be contacted by telephone, email, or visit to determine the survival status and subsequent anticancer therapy. Survival status will also be collected through medical records, national registries, or publicly available information as allowed per local regulation. If allowed by local regulations, public records may also be assessed to determine survival status. Survival status may be requested more frequently around the time of a database lock. Subjects who are not or whose designated family members are not available for this assessment should be entered as "lost to follow-up" (see [Section 7.5](#) and [Section 6.7.1](#)).

8.3 Clinical Safety Assessments

AEs will be reported and followed by the investigator as specified in [10.2](#).

Any clinically relevant changes occurring during the trial must be documented. Any clinically significant abnormalities persisting at the end of the treatment or safety follow-up will be followed by the investigator until resolution or until a clinically stable condition is reached.

The trial will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Activities, Section 1.2.

8.3.1 *Physical Examination*

The investigator or qualified designee will perform a full physical examination according to SOC during the screening period. Any relevant findings should be reported as medical history. Medical conditions should only be reported as an AE if they were assessed by the investigator or qualified designee to have been caused by a protocol-mandated procedure (eg, SBRT, tumor biopsy and/or CT scan), including washout or discontinuation of prior medications. During the treatment period, a targeted physical exam should be performed as indicated by the subject's symptoms, AEs, or other findings as determined by the investigator. New clinically significant abnormal findings should be recorded as AEs. The time points for physical examination are described in Section 1.2.

8.3.2 *Body Measurements*

8.3.2.1 *Height*

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

8.3.2.2 *Weight*

Body weight should be assessed within 48 hours prior to each dose of trial drugs.

8.3.3 *Vital Signs*

Vital signs, including temperature, pulse, blood pressure, and respiratory rate should be taken by the investigator or qualified designee as indicated in the Schedule of Activities (Section 1.2). Measurements should be taken with the subject in a supine or reclined position and recorded in the eCRF.

8.3.4 *Electrocardiograms*

A standard 12-lead ECG will be performed using local standard procedures once at screening (Section 1.2). Clinically significant abnormal findings at screening should be recorded as medical history. Further monitoring by ECG should be performed as clinically indicated.

An overall interpretation of the ECGs will be performed by the investigator, or the investigator may delegate this task to a cardiologist, if applicable.

8.3.5 *ECOG PS*

The ECOG PS will be assessed by the investigator or qualified designee at screening, prior to the infusion of GEN1042 ± pembrolizumab at each cycle start, end of treatment, and during the follow-up period as indicated in the Schedule of Activities, Section 1.2. PS will be scored using the ECOG PS scale index (Table 8-1).

Table 8-1 ECOG PS

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.

Abbreviation: ECOG PS=Eastern Cooperative Oncology Group Performance Status.

8.3.6 Clinical Laboratory Assessments

Local laboratories will be used for analysis of the tests listed in (Table 8-2), as indicated in the Schedule of Activities, Section 1.2.

Baseline safety labs (hematology and biochemistry) should be done within 14 days of the first dose of SBRT. HBV and HCV testing at baseline should be done within 28 days of the first dose of SBRT. Thereafter, safety labs (hematology and biochemistry) should be performed after completion of SBRT and within 72 hours before the start of C1D1 immunotherapy. On the other dosing days, safety labs should be performed on the same day or within 72 hours prior to each dose. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the trial.

For AE reporting of laboratory test abnormalities refer to 10.2.

Thyroid Function Testing

Thyroid function tests (TSH, free T3 and free T4) should be measured at screening, C1D1, and on D1 of every other cycle (C3D1, C5D1, C7D1, etc). At other visits, thyroid function test consists of TSH only. However, if TSH is abnormal, reflexive testing of free T3 and free T4 is to be performed. TSH, free T3, and free T4 assessments should be performed at treatment discontinuation. If drug-related toxicity is present at treatment discontinuation, repeat the thyroid function assessments at the safety follow-up visits until resolution or follow-up is sufficient.

Pregnancy Testing

WOCBP are required to have pregnancy tests performed. WOCBP must exhibit a negative serum pregnancy test during screening (within 7 days prior to C1D1) and negative urine pregnancy tests (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 72 hours prior to Day 1 of each cycle and at the 30-day safety follow-up visit. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Pregnancy testing will be done locally and as outlined in Section 1.2.

Table 8-2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology (local test)	Hematocrit	WBC count with differential: Basophils monocytes Eosinophils neutrophils Lymphocytes		
	Hemoglobin			
	Platelet count			
	RBC count			
Biochemistry (local test)	ALT	BUN	GGT	Phosphate
	Albumin	Calcium	Glucose	Potassium
				Sodium
	Alkaline phosphatase	Chloride	HbA1C	Total and direct bilirubin
	Amylase	C-reactive protein	LDH	Total protein
	AST	Creatinine (and estimated Clcr) ^a	Lipase	Uric acid
			Magnesium	
PSA ^d				
Coagulation factors (local test)	aPTT	INR	PT	
Urinalysis (local test)	Leukocytes	Protein	Pregnancy test ^c	
Endocrine (local test)	Free T3 ^b	Free T4 ^b	TSH	
Other screening tests (local test)	HBV, HCV per local standard Serum β-hCG ^e			

Abbreviations: ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β -hCG=beta-human chorionic gonadotropin; BUN=blood urea nitrogen; Clcr=creatinine clearance; EOT=end-of-treatment; GGT=gamma-glutamyltransferase; HbA1C=glycosylated hemoglobin test; HBV=hepatitis B virus; HCV=hepatitis C virus; INR=international normalized ratio; LDH=lactate dehydrogenase; MDRD=Modification of Diet in Renal Disease; PSA=prostate-specific antigen; PT=prothrombin time; RBC=red blood cell; T3=total triiodothyronine; T4=free thyroxine; TSH=thyroid stimulating hormone; WBC=white blood cell.

a. Estimate creatinine clearance using the abbreviated MDRD equation.

b. Free T3/T4 is acceptable if considered local standard. Thyroid function tests (TSH, free T3 and free T4) should be measured at screening, C1D1, and on D1 of every other cycle (C3D1, C5D1, C7D1, etc). At other visits, thyroid function test consists of TSH only. However, if TSH is abnormal, reflexive testing of free T3 and free T4 is to be performed.

c. Serum β -hCG will be collected at screening and urine tests should be performed within 72 hours of Day 1 of each cycle, at the EOT visit, and at the 30-day safety follow-up visit. A urine test may be performed during an unscheduled visit at the investigator's discretion, if clinically indicated.

d. PSA will only be measured for prostate cancer patients.

8.4 Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical trials are crucial for the protection of trial 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 trials 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 10.2.

8.4.1 *Definition of Adverse Events and Serious Adverse Events*

The definitions of AEs, SAEs, AESIs, as well as attribution definitions; severity criteria; special reporting situations; and procedures, are provided in [10.2](#).

8.4.2 *Adverse Event Reporting*

AEs and SAEs (see definitions in [10.2](#)) will be documented from the first fraction of SBRT until 30 days and 90 days after the last dose of trial treatment, respectively, as documented in the Schedule of Activities, Section [1.2](#).

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 infusion should only be reported as AEs if they were assessed by the investigator to be caused by a protocol-mandated procedure (eg, SBRT, tumor biopsy, and/or CT scan), including washout or discontinuation of prior medications. Any events not related to a trial procedure will be reported as medical history.

For details regarding follow-up of AEs and SAEs, see Section [8.4.6](#).

8.4.3 *Events Requiring Immediate Reporting*

The events that require immediate reporting are detailed in the subsections below.

8.4.3.1 *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 such AE was reported, noted, or recognized.
- The principal investigator's or any investigator personnel's receipt of the test results.
- Other information from which such development was reported, noted, or recognized or
- A new cancer that is not a metastasis of the disease under trial.

8.4.3.2 *Drug-Induced Liver Injury*

All DILI events are considered as medically significant events and must be reported to the sponsor as SAEs within 24 hours after sites become aware of the events. Per available regulatory guidance (FDA, 2009b), Hy's law for identification of potential DILI is defined as:

- Aminotransferase (ALT and/or AST) $>3 \times \text{ULN}$; and
- Total bilirubin $>2 \times \text{ULN}$, without initial findings of cholestasis (elevated serum alkaline phosphatase); and
- No other reason can be found to explain the combination of increased ALT/AST and total bilirubin.

8.4.3.3 *Overdose/Medication Errors*

An overdose is defined as a subject receiving a dose of GEN1042 in excess of 10% of that specified in this protocol. Overdose of pembrolizumab is defined as any dose of 1000 mg or ≥ 5 times the indicated dose.

All cases of overdose, whether associated with an AE or not, must be reported to the sponsor within 24 hours of knowledge of the event (see additional details in Section 8.5).

Medication errors (including infusion rate errors) and uses outside what is foreseen in the protocol, including misuse and abuse of the product, whether associated with an AE or not, should be reported within 24 hours of knowledge of the event.

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. 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.

Once informed consent is obtained, the pregnancy must be followed up to determine the 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 trial treatment 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.

8.4.4 *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 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 8.4.3.1).

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.

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

8.4.5.1 *Progression or Death*

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

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

That is, the terms “Disease Progression”, “Progression of Disease”, “Malignant Disease Progression”, or “Malignant Neoplasm 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 of progression 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 [10.2](#), under the definition of SAE, for additional reasons when hospitalizations should not be reported as SAEs.

8.4.5.2 *Unrelated Procedures*

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

8.4.6 *Follow-up of Adverse Events and Serious Adverse Events*

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

All SAEs 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.

Any new primary cancer (that is not a metastasis of the cancer under trial), should be reported after the safety follow-up period. All other SAEs judged by the investigator as related to trial drug should be reported after the safety follow-up period.

8.4.7 *Warnings and Precautions*

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

8.5 *Treatment of Overdose*

Rescue medication to reverse the action of GEN1042 is not available. In case of overdose, medication errors, misuse, and/or abuse of the trial drug, subjects should receive supportive care according to local guidelines and potential side effects of GEN1042 should be treated symptomatically.

No specific information is available on the treatment of overdose of pembrolizumab (>5 times the recommended dose). In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event of an overdose, the investigator should:

- Contact the sponsor's medical monitor immediately (see Section [8.4.3](#))
- Closely monitor the subject for any AE/SAE and laboratory abnormalities
- Obtain a 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

8.6 *Pharmacokinetics*

Blood samples will be collected for measurement of serum concentrations of GEN1042 as specified in [Table 1-2](#). The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of GEN1042. Venous blood samples will be collected, and each serum sample will be divided into aliquots. Samples collected for analyses of serum concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period. Genetic analyses will not be performed on these plasma samples. Subject confidentiality will be maintained.

8.7 *Biomarkers*

8.7.1 *Biomarker Sample Collection*

Samples for biomarker and pharmacodynamic analyses will be collected as specified in [Table 1-2](#). 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 or laboratory manual).

8.7.1.1 Biomarker Assessments in Tumor Samples

In part 1, all subjects must provide a tumor tissue sample (FFPE blocks/slides) from archival tissue or from biopsy collected after failure/stop of last prior treatment and prior to SBRT, preferably derived from advanced disease stage. Biopsy tissue should be from 1 radiation assigned and 1 non-radiation assigned lesion collected during the screening period. The first on-treatment imaging assessment and on-treatment biopsy must be done between C2D15 and C3D1 where it is considered feasible without a risk of complications. The imaging assessment must be prior to the biopsy. All subjects should provide a PD or treatment discontinuation biopsy whenever feasible.

In part 2, all subjects must provide a mandatory tumor biopsy (FFPE sample only; aspirates are not acceptable) which contains tumor tissue and is taken after failure/stop of last prior treatment and prior to SBRT. Biopsy tissue should be from 1 radiation assigned and 1 non-radiation assigned lesion collected during the screening period. Documentation of the recent biopsy shipment must be submitted to the sponsor prior to randomization. In addition to the newly obtained biopsy, the latest available archival tumor tissue sample should be collected if available. Where it is not feasible to meet the required criteria for new FFPE tumor biopsy, the sponsor medical monitor's approval for enrollment is needed. If feasible, an on-treatment biopsy will also be collected from the same lesions biopsied at screening (1 radiation assigned and 1 non-radiation assigned). All subjects should provide a PD or treatment discontinuation biopsy whenever feasible.

During the trial, if any additional tumor biopsies are collected that are part of normal clinical practice, a portion of these tumors should be provided for biomarker testing as described below.

Biomarker analyses in tumor samples at baseline and during treatment may help confirm GEN1042's MoA and enable the identification of biomarkers predictive of response to trial treatment. Tumor biopsies will be evaluated for target expression (ie. protein, DNA or RNA), as well as molecular profiling to identify potential mechanisms of tumor response and/or treatment-induced changes in the immune microenvironment.

8.7.1.2 Protein Expression Analyses

Expression of proteins 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.

8.7.1.3 *RNA Expression Analyses*

RNA sequencing may be performed on tumor biopsies to determine target expression levels, immune signatures based on gene expression, and expression of other genes related to GEN1042's MoA CCI or disease biology.

8.7.1.4 *DNA Analyses*

Tumor biopsies may also be analyzed CCI

8.7.1.5 *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 disease biology, efficacy and/or MoA for GEN1042, pembrolizumab, or SBRT. Assessments will be performed at baseline (before infusion at C1D1) and at later cycles during treatment to enable correlation analyses.

8.7.1.6 *Immunophenotyping Analyses*

Immunophenotyping may be performed CCI at baseline and during treatment at planned visits so changes associated with the MoA of GEN1042 and in combination with pembrolizumab, subject response to trial treatment, and disease biology can be evaluated.

8.7.1.7 *Cytokine (Soluble Factors) Analyses*

Measurement of soluble immune mediators CCI will be performed in plasma or serum samples collected at baseline and at different times during treatment at planned visits to assess changes associated with the MoA of GEN1042.

8.7.1.8 CCI RNA Analyses and Changes in ctDNA CCI

CCI

8.7.1.9 CCI

8.8 Immunogenicity

Venous blood samples will be drawn for analysis of ADAs as per the time points specified in the Schedule of Activities (Section [1.2](#)).

Serum samples will be screened for ADAs binding to trial treatment 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.

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 randomization list will be prepared by the biometrics vendor. Although the trial is open-label, analyses or summaries by treatment arm in the randomized phase 2 part will be limited and documented.

9.1 Statistical Hypothesis

No formal statistical hypothesis will be tested.

9.2 Sample Size Determination

Up to 48 subjects are expected to be included in part 1 (dose finding). A modified 3+3 design will be used to evaluate and determine the MTD and RP2D of GEN1042 alone or in combination with concurrent pembrolizumab following SBRT.

For part 2 (randomized 2-arm), the enrollment of 20 subjects per arm will allow an estimation of ORR with a 95% CI of (3.2%, 37.9%) if the observed ORR is 15%, and a 95% CI of (11.9%, 54.3%) if the observed ORR is 30%.

9.3 Populations for Analyses

The FAS, which consists of all subjects enrolled and treated with at least 1 dose of trial treatment (GEN1042 ± pembrolizumab), will be used for the safety, efficacy, and PK analyses.

The dose-determining analysis set includes all subjects from the FAS in part 1 who met the minimum exposure criterion, had sufficient safety evaluations, and finished the DLT observation period (ie, 1 cycle of 21 days), or who experienced a DLT during cycle 1 (the first 21 days of dosing).

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.

The primary analysis is planned for when the last subject has undergone 3 tumor assessments. The timing of the primary analysis may be revised if the duration of treatment differs from that expected. The final analysis will be conducted when all subjects have discontinued treatment and have completed required follow-up visits. At this time, a final data sweep will be performed to determine the progression and vital status of previously discontinued subjects.

9.4.1 *Subject Demographics and Baseline Characteristics*

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment arm for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical histories at baseline will be summarized by system organ class and preferred term by treatment arm.

9.4.2 *Efficacy Analyses*

9.4.2.1 *Abscopal Response and Objective Response Rate*

Abscopal response in non-irradiated target lesions as assessed by investigator is the primary endpoint in part 2 and secondary endpoint in part 1. Abscopal response is defined as a reduction of at least 30% in diameter of the best responding non-irradiated target lesion.

Abscopal response rate will also be calculated and is defined as the proportion of subjects with abscopal response. Subjects who are non-evaluable or without any available response assessments are counted as non-responders.

ORR in irradiated and non-irradiated tumor lesions as assessed by investigator per RECIST v1.1 are secondary endpoints for both part 1 and part 2. In addition, abscopal response rate will also be summarized for part 1.

ORR is defined as the proportion of subjects with a confirmed BOR of CR or PR according to RECIST 1.1 (see 10.5). Subjects who are non-evaluable or without any available response assessments are counted as non-responders. A minimum of 5 weeks from baseline is required for a BOR of SD.

Abscopal response rate/ORR and its exact 2-sided 95% CI, using the Clopper-Pearson method, will be presented by regimen (part 1) or treatment arm (part 2).

DCR, defined as the proportion of subjects with a BOR of CR, PR, and SD, will be summarized similar to ORR.

9.4.2.2 *Duration of Response*

DOR is defined as the time from the onset date of response to the date of the first documented progression or death due to any cause. It only applies to the subset of subjects in the FAS who respond, ie, have confirmed BOR of CR or PR. The Kaplan-Meier method will be used to estimate the survival functions for DOR in each treatment arm and the estimated median will be presented with 95% CI. Subjects without evidence of radiographic disease progression or death will be censored at the date of the last adequate tumor assessment prior to data cut-off or start of new anticancer therapy in accordance with the FDA Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA, 2009); see 10.6 for more details.

9.4.2.3 *Progression-Free Survival*

PFS is defined as the time from the date of randomization (or date of first administration of GEN1042 ± pembrolizumab treatment for subjects in part 1) to the date of the first documented progression or death due to any cause.

The Kaplan-Meier method will be used to estimate the PFS functions in each treatment arm. Subjects without evidence of radiographic disease progression or death will be censored at the date of the last adequate tumor assessment prior to data cut-off or start of new anticancer therapy in accordance with the FDA Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics; see [10.6](#) for more details.

9.4.2.4 *Overall Survival*

OS is defined as the time from date of randomization (or date of first administration of GEN1042 ± pembrolizumab treatment for subjects in part 1) to date of death due to any cause.

The Kaplan-Meier method will be used to estimate the survival functions in each treatment arm. Subjects without a documented death at the time of analysis will be censored at the date of the latest date the subject was known to be alive (on or before the cut-off date).

One-year (12-month) OS will be estimated.

9.4.3 *Safety Analyses*

For all safety analyses, the FAS will be used. All listings and tables will be presented by regimen (part 1) or treatment arm (part 2).

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

1. Pre-treatment period: from day of subject's informed consent to the day before the first administration of GEN1042 ± pembrolizumab
2. On-treatment period: from day of first administration of GEN1042 ± pembrolizumab to 30 days after last dose of trial drug (90 days after last dose of trial drug for SAEs only)
3. Post-treatment period: starting at 1 day after the end of the on-treatment period.

AEs that started from the first fraction of SBRT and before the first administration of trial drug will be summarized separately.

9.4.3.1 *Adverse Event*

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the MedDRA. Treatment-emergent AEs are AEs that started or worsened during the on-treatment period. All reported AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by regimen (part 1) or treatment arm (part 2).

The AEs will be summarized by system organ class and/or preferred term, severity (based on grades of the NCI-CTCAE v5.0), type of AE, and relationship to trial treatment.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, discontinue trial treatment due to an AE, or who experience a severe AE or an SAE.

Additional details are provided in the SAP.

9.4.3.2 Clinical Laboratory Tests

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

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

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

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades, if applicable, and the classifications relative to the laboratory normal ranges.

For laboratory tests where grades are defined by the CTCAE:

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

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

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

9.4.3.3 Other Safety Data

Electrocardiogram

12-lead ECGs including PR, QRS, QT, and RR intervals will be obtained at baseline for each subject during the trial. Additional ECGs may be obtained when clinically indicated. ECG data will be read and interpreted locally.

Categorical analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline may be presented. In addition, a listing of these subjects by treatment arm will be produced.

Vital signs

Data on vital signs will be tabulated and listed; notable values will be flagged.

9.4.4 Pharmacokinetic Analyses

The PK of GEN1042 only, as monotherapy or in combination with pembrolizumab following SBRT, will be evaluated in a model-based approach.

Samples will be used to evaluate the PK and immunogenicity of GEN1042. Remaining samples collected for analyses of GEN1042 concentration may also be used to evaluate other safety, efficacy, or biomarker laboratory parameters to address concerns arising during the trial.

Results of PK analyses may be presented in a separate report.

9.4.5 Biomarker Analyses

Biomarker analyses in this trial are exploratory endpoints CCI [REDACTED] and focus on understanding the collective MoA of GEN1042 ± pembrolizumab following SBRT, identifying potential pharmacodynamic markers to help identify the appropriate dose and schedule of GEN1042 in combination, and identifying potential predictive markers that may be further validated in prospective trials with GEN1042 ± pembrolizumab following SBRT.

Biomarkers, such as target expression, peripheral immune cell populations, and cytokine measurements will be tabulated for all subjects who had samples collected and testing performed. Biomarker assessments will be summarized by timepoint using descriptive statistics. Changes in biomarker parameters, as compared to baseline, will be calculated and analyzed for association with relevant clinical endpoints such as objectives response, PFS, or OS. Subgroup analyses may be performed to evaluate differences between biomarker parameters in groups of responders and non-responders or other clinically relevant subgroups, and to evaluate the associations between biomarker parameters and specific clinical endpoints. Univariate and multivariate analyses, as well as pathway analyses may also be performed if applicable. Any pharmacodynamic measures will be listed, tabulated, and plotted as appropriate. Subjects may be grouped by cohort, dose schedule, or clinical response.

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

9.4.6 Immunogenicity Analyses

GEN1042 ADA titers will be listed and positive/negative host immune response to GEN1042 and the presence of neutralizing antibodies may be summarized (positive/negative). Presence of PK concentrations above a certain threshold that depends on the drug tolerance of the ADA assay, at the same time as the ADA sample may make the ADA undetectable and hence render nonconclusive. The association between positive/non-positive ADA and PK (pre-dose, AUC, C_{max}), major safety signals (CTCAE $\geq$ grade 3) and efficacy information (change in tumor size by CT scan) will be explored.

9.4.7 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate with a nominal 95% CI for the abscopal response rate, the primary endpoint in part 2, will be estimated and plotted within each category of the following classification variables:

- Age category (eg, <65, ≥65 years)
- Sex (female, male)
- Race category (where permitted)
- ECOG PS
- Histology
- Smoking status
- Number of metastatic sites
- Location of metastasis (such as liver, lung, etc)
- Prior anticancer therapy
- CPI naive vs CPI experienced

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

9.5 Interim Analyses

If commenced, in part 2 of the trial, 1 interim analysis for futility is planned after approximately 10 subjects per treatment arm have been treated and had at least 2 response assessments post-baseline. Enrollment will not be stopped for futility analysis. If there is 1 or fewer response in the first 10 subjects, the corresponding treatment arm(s) may be stopped (non-binding). Otherwise, 10 additional subjects will be accrued for a total of approximately 20 subjects per treatment arm.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and Ethical Considerations

The principles of the Declaration of Helsinki, the consolidated ICH-GCP, and applicable regulations and national law(s) (eg, 21 CFR and European regulation 536/2014 for clinical trials) in the country(ies) where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

ICH GCP E6(R2) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the trial data are credible.

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

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

10.1.2 Investigator Responsibilities

The investigator is responsible for ensuring that the trial is performed in accordance with the protocol, ICH GCP E6(R2), and applicable regulatory and country-specific requirements. This includes supervision of the trial and staff. Delegation of responsibilities should be to only qualified staff and should be documented. In case the investigator is unavailable (eg, on vacation), the investigator should assure that a qualified, trained deputy physician is available for medical care of the subjects. The investigator shall notify the sponsor immediately of any serious breach of ICH GCP E6(R2), the protocol, or any regulation where required.

10.1.3 Independent Ethics Committee

This trial will be undertaken only after the IEC and the National Agency for the Safety of Medicines and Health Products have 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.

10.1.4 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.5 Administrative Procedures

10.1.5.1 Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects (see 10.1.1) 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.

10.1.5.2 Regulatory Documentation

This protocol and any amendments must be submitted to the appropriate regulatory authorities in each respective country, in accordance with local regulations. A trial may not be initiated until all local regulatory requirements are met.

10.1.5.3 *Subject Identification, Enrollment, and Screening Logs*

The investigator agrees to complete a subject identification log to permit easy identification of each subject during and after the trial. This document will be reviewed by the sponsor trial-site contact for completeness.

The subject identification log will be treated as confidential and will be filed by the investigator in the Investigator Site file and will never be transferred to the sponsor or any third parties. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the trial will identify subjects by their unique subject identifier.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the trial.

10.1.6 *Informed Consent Process*

The ICF(s) that is/are used must be approved by the reviewing IEC/IRB and be in a language that the subject can read and understand. The ICF should be in accordance with principles that originated in the Declaration of Helsinki, ICH GCP E6(R2), applicable regulatory requirements, and sponsor policy.

It is the personal responsibility of the investigator or an authorized member of the trial-site personnel to explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial, and any discomfort participation in the trial may entail.

Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time without justifying the reason. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of their disease. 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 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 is authorizing such access, including permission to obtain information about survival status, and agrees to allow their trial physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, [and subsequent disease-related treatments, or to obtain information about survival status].

The subject will be given sufficient time to read the ICF and the opportunity to enquire about details of the trial prior to deciding whether to participate in the trial. After this explanation and before any trial-specific procedure is performed, consent should be appropriately documented by means of the subject's personally dated signature.

Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA and EU GDPR requirements, where applicable, and the IRB/IEC or trial center. The investigator or authorized person obtaining the

informed consent must also sign and date the ICF. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

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

A 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.

10.1.7 Data Protection

The investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF or any other documents submitted to the sponsor/sponsor's representative, the subjects will not be identified by their names, but by an identification code, which consists of an assigned number in the trial. The confidential subject identification code and the signed 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 is only stored on information technology systems and networks that are protected against virus, malware, and unauthorized access.
- Data is backed-up at regular intervals. In case of a data breach, a clear allocation of roles and responsibilities for managing the data breach, including notifying affected subjects and authorities, has been established in order to mitigate any adverse impact on the subjects.

Additional technical security measures implemented include that:

- All data 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 includes explicit consent or description of other legal basis for the processing of personal data for the purpose of the trial and for the investigator/institution to allow direct access to original medical records (source data/documents) for trial-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries, as specified in the ICF.

The subject has the right to request access to their personal data and the right to request rectification of any data that are not correct or complete by contacting the investigator. Reasonable steps will be taken by the investigator to respond to such a request, taking into consideration the nature of the request, the conditions of the trial, the clinical trial agreement including any other relevant agreement, and applicable laws and regulations. The investigator will inform and work together with the sponsor when handling such requests.

In case of a potential data breach of the personal data, the investigator will inform the sponsor immediately and will contain the breach from spreading, where possible. Investigator and sponsor will work together to assess the risk to the individuals concerned, based on the circumstances of the case, including which data was involved, what security measures were in place (for instance, if the data was encrypted or pseudonymized), who might have accessed the data, etc.

Based on this assessment, the data breach might be reported to the relevant authorities and/or the individuals concerned. Mitigating actions will be taken to avoid this event from reoccurring.

10.1.8 Committees Structure

Dose Escalation Committee and Safety 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 part 1.

The schedule of DEC meetings will depend on the completion of DLT(s) evaluation period(s) (period is defined for each trial).

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 subsequent treatment doses may also be monitored. The SC may be consulted if needed.

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

10.1.9 *Dissemination of Clinical Trial Data*

The protocol information will be registered in a publicly accessible database (eg, clinicaltrials.gov, CTIS, and/or other national registries/health authority websites). In addition, after trial completion (defined in Section 4.4.2) and finalization of the CSR, the results of this trial will be submitted for disclosure and posted in a publicly accessible database of clinical trial results as required by local regulations (eg, clinicaltrials.gov, CTIS).

Exploratory biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to subjects or investigators. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

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

10.1.10.1 *Data Quality Management*

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate trial sites, review of protocol procedures with the investigator and trial-site personnel before the trial, and periodic monitoring visits by the sponsor (or sponsor's delegate). Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided. The sponsor/CRO will review eCRFs for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the trial database, the data will be reviewed for accuracy and consistency with the data sources.

10.1.10.2 *Record Retention*

In compliance with ICH GCP E6(R2), the investigator/institution will maintain all eCRFs and all source documents, as well as a source document location list, that support the data collected from each subject, as well as all trial documents as specified in ICH GCP Guideline Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for 25 years after end of trial. These documents will be retained for a longer period if required by the applicable regulatory requirements. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Medical Records (subjects' hospital record) is retained/archived according to applicable local regulation.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a qualified and trained person who will accept the responsibility. The sponsor must be notified in writing of the name

and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this trial, the investigator/institution must permit access to such reports.

10.1.10.3 Monitoring

The sponsor will use a combination of remote and on-site monitoring to monitor this trial. The sponsor or delegate will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial-site visit log that will be kept at the trial site. The first post-initiation visit will be made as soon as possible after enrollment (ie, the first subject has signed the ICF) has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and trial-site personnel and are accessible for verification by the sponsor trial-site contact. If electronic records are maintained at the trial site, the method of verification must be discussed with the trial-site personnel. Where allowed in accordance with local regulations, or in the event of a national emergency, and in agreement with the investigator, remote source data verification or source data review may be performed.

The investigator must permit the monitor access to all source data, including electronic medical records, and/or documents with the purpose of verifying that the data recorded in the eCRF are consistent with the original source data.

Findings from this review of eCRFs and source documents will be discussed with the trial-site personnel. The sponsor expects that, during monitoring visits, the relevant trial-site personnel will be available, the source documentation will be accessible, and a suitable environment will be provided for review of trial-related documents. The monitor will meet/talk with the investigator on a regular basis during the trial to provide feedback on the trial conduct.

In addition to on-site monitoring visits, remote contact can occur. It is expected that during these remote contacts, trial-site personnel will be available to provide an update on the progress of the trial at the site.

10.1.10.4 On-Site Audits and Inspections

Representatives of the sponsor's clinical quality assurance department may visit the trial site at any time during or after completion of the trial to conduct an audit of the trial in compliance with regulatory guidelines and company policy. These audits will require access to all trial records, including source documents, for inspection and comparison with the eCRFs. Subject privacy must, however, be respected. The principal investigator and trial-site personnel are responsible for being present and available for consultation during routinely scheduled trial-site audit visits conducted by the sponsor or its designee(s).

Similar procedures for inspections may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if

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

10.1.11 Source Documents and Case Report Form Completion

10.1.11.1 Source Documentation

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. At a minimum, the type and level of detail of source data available for a subject should be consistent with that commonly documented at the trial site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial, described in the monitoring guidelines (or equivalent), and captured in a source data verification log at site.

For each subject, the investigator must indicate in the hospital/medical source records that the subject participates in this trial and the date of obtaining the ICF. The records should document data on the condition of the subject at the time the subject is enrolled in the trial, to enable verification of eligibility. 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.
- Subject identification 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 addition to the source data in medical records, data may be recorded directly electronically (eg, ECGs, PROs, etc). Such data are considered source data and are accessible by both the investigator and sponsor.

The author of an entry in the source should be identifiable.

Information included in the subject's hospital records may be subject to local regulations. If there is a discrepancy between local requirements and the protocol, local regulations should be followed.

10.1.11.2 Case Report Form Completion

CRF data will be transcribed into an EDC system by trial-site personnel from the source documents. Both EDC and other electronically captured trial data will be transmitted in a secure manner to the sponsor within agreed upon time frames.

Data relating to the trial must be documented and reported in English. Trial site personnel must complete the CRF as soon as possible after the data are available and preferably within **5 days**. Source data and the CRFs should be available for review at the next scheduled monitoring visit.

All eCRF entries, response to queries, corrections, and alterations must be made by the investigator or other authorized trial-site personnel. 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:

- Trial-site personnel can make corrections in the EDC tool at their own initiative or as a response to an auto query (generated by the EDC tool).
- The monitor can generate a query for resolution by the trial-site personnel.
- The sponsor or designee can generate a query for resolution by the trial-site personnel.

10.1.12 Trial and Site Start and Closure

The first act of recruitment is the first subject screening visit.

The sponsor reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's guidance documents/trial plans, ICH GCP E6(R2), and applicable regulatory requirements.

- Inadequate recruitment of subjects by the investigator.
- Discontinuation of further trial drug development. The sponsor may, based on available data, discontinue further development of GEN1042. Following trial termination, the sponsor will make their best effort to provision post-trial access to GEN1042 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 assure 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.

10.1.13 Publication Policy

All information, including but not limited to information regarding GEN1042 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 biomarker research data, generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this trial and will not use it for other purposes without the sponsor's prior written consent. CROs involved in the trial are not permitted to publish without the sponsor's prior written approval.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of GEN1042, and thus may be disclosed 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.

The results of the trial will be reported in a CSR generated by the sponsor and will contain data from all trial sites that participated in the trial. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the trial will be used to determine a coordinating investigator for the CSR (eg, when a signature by a coordinating investigator is required). Results of exploratory biomarker analyses performed after the CSR has been issued will be reported in a separate report and will not require a revision of the CSR. Trial subject identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines ([Battisti et al., 2015](#); [ICMJE, 2010](#); [ICMJE, 2016](#); [ICMJE, 2019](#)), the sponsor

in conjunction with any collaborative group(s), shall have the right to publish such primary (multicenter) data and information as per the pre-specified and approved publication plan. If an investigator wishes to publish information from the trial, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter trial designs and sub-trial approaches, secondary results generally should not be published before the primary endpoints of a trial have been published. Similarly, investigators will recognize the integrity of a multicenter trial by not submitting for publication data derived from the individual trial site until the combined results from the completed trial have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter trial publication. Authorship of publications resulting from this trial will be based on the guidelines on authorship, such as those described in the current version of 'Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals' (ICMJE Recommendations) <http://www.icmje.org/recommendations/>), which state that the named authors must have made a significant contribution to the design of the trial or analysis and interpretation of the data, provided critical review of the paper, given final approval of the final version, and agreed to be accountable for all aspects of the work.

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

10.2.1 Definitions

10.2.1.1 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.

10.2.1.2 Definition of Serious Adverse Events

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

- Is fatal or life-threatening¹
- 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 hospitalization²

¹The 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.

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

- Routine treatment or monitoring of the underlying disease, not associated with any deterioration in the condition
- Solely due to progression of the underlying cancer
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the underlying disease and has not worsened since signing the ICF
- Social reasons and respite care in the absence of any deterioration in the subject's general condition

- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above.

10.2.1.3 Definition of Adverse Events of Special Interest

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

There are no AESIs defined for this protocol.

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. The CTCAE v5.0 category of "infusion-related reaction" should be used to describe GEN1042 or GEN1042/pembrolizumab reactions, unless the investigator considers another category, such as "allergic reaction", "anaphylaxis", or "cytokine release syndrome" more appropriate in the specific situation. For IRRs, the causality of the event should be judged as "related" to either GEN1042 or GEN1042/pembrolizumab combination by the investigator.

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.

10.2.2 Procedures for Recording and Reporting

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

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

10.2.3 *Evaluation of Adverse Events*

Severity

Toxicities will be graded for severity according to the NCI-CTCAE, v5.0.

Relationship to the Investigational Medicinal Product

The investigator must assess whether or not the event is related to GEN1042 or GEN1042/pembrolizumab combination. The relationship is to be judged using the following terms:

- Related
- Not related

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

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

Follow up of Adverse Events and Serious Adverse Events

This is trial specific and defined in Section 8.4.6, Follow-up of Adverse Events and Serious Adverse Events.

10.2.4 *Annual Safety Reporting by Sponsor*

The sponsor will submit a single Annual Safety Report for all Genmab trial drugs in this clinical trial. The rationale for a single submission is all other trial drugs are non-Genmab compounds.

10.3 Appendix 3: Definition of Reproductive Potential and Contraception

Female subjects of reproductive potential must agree to use adequate contraception during and for at least 1 month after receiving the last dose of GEN1042 or for at least 4 months after receiving the last dose of pembrolizumab. Adequate contraception is defined as highly effective methods of contraception (see Table 10-1). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year when used consistently and correctly.

In this trial, subjects are considered to have reproductive potential unless they are postmenopausal or permanently sterile.

- A postmenopausal state is defined as no menses in subjects >45 years of age for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a post-menopausal 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 at least 1 month after receiving the last dose of GEN1042 or for at least 4 months after receiving the last dose of pembrolizumab.

All male subjects must agree not to donate any sperm from the day of the first administration of GEN1042 until at least 1 month after receiving the last dose of GEN1042 or for at least 4 months after receiving the last dose of pembrolizumab.

Table 10-1 Highly Effective Methods of Contraception

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

- a. Hormonal contraception may be susceptible to interaction with GEN1042, 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](#)).

10.4 Appendix 4: Sample Storage and Destruction

Any sample collected according to the Schedule of Activities (Section 1.2) 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 disease biology, the dose response and/or prediction of response to GEN1042, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained; but are not necessarily reported as part of this trial. Samples can be retained for up to 5 years after the last subject receives the first dose of trial treatment. Samples will be destroyed after the 5-year retention period.

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required trial and subject number so that any remaining samples and any other components from the cells can be located and destroyed. 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 10.1.7 for subject confidentiality.

10.5 Appendix 5: Best Overall Response When Confirmation of CR and PR Required per RECIST 1.1

Overall Response First Time Point	Overall Response Subsequent Time Point (≥ 4 Weeks from First Time Point)	Best Overall Response with Confirmation
CR	CR	CR
CR	PR	Query site – this should never happen.
CR	SD	SD if CR is at least 5 weeks from first dose, otherwise PD
CR	PD	SD if CR is at least 5 weeks from first dose, otherwise PD
CR	NE	SD if CR is at least 5 weeks from first dose, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if PR is at least 5 weeks from first dose, otherwise PD
PR	NE	SD if PR is at least 5 weeks from first dose, otherwise NE

Abbreviations: CR=complete response; NE=non-evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

10.6 Appendix 6: Censoring Rules (FDA Guidance 2015, Clinical Trial Endpoints for the Approval of NSCLC Drugs and Biologics)

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Date of first dose	Censored
Progression documented between scheduled visits	Date of progression assessment	Progressed
No progression	Date of last adequate assessment	Censored
New anticancer treatment started	Date of last adequate assessment with documented non-progression before start of new treatment	Censored
Death before first tumor assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed tumor assessment	Date of last adequate assessment with documented non-progression	Censored

Abbreviations: FDA=Food and Drug Administration; NSCLC=non-small cell lung cancer.

10.7 Appendix 7: Grading of Cytokine Release Syndrome

Harmonized definitions and grading criteria for CRS, per the American Society for Transplantation and Cellular Therapy (ASTCT), formerly American Society for Blood and Marrow Transplantation, (ASBMT), are presented below.

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever ¹	≥38.0°C	≥38.0°C	≥38.0°C	≥38.0°C	Death due to CRS in which another cause is not the principal factor leading to this outcome
With hypotension ²	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring ≥ 2 vasopressors (excluding vasopressin)	
And/or hypoxia ²	None	Requiring low-flow (≤6 L/minute) nasal cannula or blow-by	Requiring high-flow (>6 L/minute) nasal cannula, facemask, nonrebreather mask, or venturi mask	Requiring positive pressure ventilation ³ (eg, CPAP, BiPAP, intubation and mechanical ventilation)	

Abbreviations: BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; CTCAE =Common Terminology Criteria for Adverse Events.

Note: Organ toxicities or constitutional symptoms associated with CRS may be graded according to CTCAE but they do not influence CRS grading.

1. Fever is defined as temperature ≥38.0°C not attributable to any other cause, with or without constitutional symptoms (eg, myalgia, arthralgia, malaise). In subjects who have CRS and are receiving antipyretics, anticytokine therapy, and/or corticosteroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
2. CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a subject with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. Both systolic blood pressure and mean arterial pressure are acceptable for blood pressure measurement. No specific limits are required, but hypotension should be determined on a case-by-case basis, accounting for age and the subject's individual baseline, ie, a blood pressure that is below the normal expected for an individual in a given environment.
3. Intubation of a subject without hypoxia for the possible neurologic compromise of a patent airway alone or for a procedure is not by definition grade 4 CRS.

Source: (Lee et al., 2019).

10.8 Appendix 8: CRS Management Guidance

Grading of Cytokine Release Syndrome Based on the American Society for Transplantation and Cellular Therapy (ASTCT)^a Guidelines

CRS Grade ^a	Supportive Care	Anticytokine Therapy	Glucocorticoids
Grade 1	<p>Hold GEN1042 ± pembrolizumab until resolution of CRS.</p> <p>In-person evaluation by medical professional, ideally at site or center with experience managing CRS.</p> <p>Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve.</p> <p>Supportive care per institutional standard of care (antipyretics and IV hydration) Closely monitor neurologic status</p>	<p>Consider anticytokine therapy in certain cases, eg, advanced age, high tumor burden, circulating tumor cells, fever refractory to antipyretics.</p> <p>Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)</p>	<p>Dexamethasone 10-20 mg per day (or equivalent) may be initiated.</p> <p>Note: In case of concurrent ICANS, initiation of corticosteroids is highly recommended</p>
Grade 2	<p>Hold GEN1042 ± pembrolizumab until resolution of CRS.</p> <p>In-person evaluation by medical professional, ideally at site or center with experience managing CRS.</p> <p>Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve.</p> <p>Continuous cardiac telemetry and pulse oximetry as indicated IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids Supplemental oxygen as indicated</p>	<p>Anticytokine therapy recommended^c If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy.</p> <p>Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)</p>	<p>Consider dexamethasone 10-20 mg per day (or equivalent).</p> <p>Note: In case of concurrent ICANS, initiation of corticosteroids is highly recommended.</p>
Grade 3	<p>Hold GEN1042 ± pembrolizumab until resolution of CRS. May resume at a lower dose of GEN1042 upon discussion with the sponsor.</p> <p>Permanently discontinue GEN1042 ± pembrolizumab if vasopressor is used and/or</p>	<p>Anticytokine therapy recommended^c If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy.</p> <p>Note: In case of concurrent ICANS, choose alternative to</p>	<p>Dexamethasone (eg, 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.</p>

CRS Grade ^a	Supportive Care	Anticytokine Therapy	Glucocorticoids
	<p>CRS occurred together with MAS and/or HLH.</p> <p>In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum antibiotics.</p> <p>Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Management in intensive care unit.</p> <p>Vasopressor support and/or supplemental oxygen. Consider cardiac echocardiogram. IV fluids as indicated.</p>	<p>tocilizumab (eg, siltuximab, anakinra)</p>	
Grade 4	<p>Permanently discontinue GEN1042 ± pembrolizumab. In-person evaluation by medical professional, ideally at site or center with experience managing CRS.</p> <p>Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve.</p> <p>Management in intensive care unit.</p> <p>Mechanical ventilation and/or renal replacement therapy may be required</p> <p>Vasopressor support as indicated IV fluids as indicated.</p> <p>Consider and assess for development of MAS/HLH^b, including monitoring of fibrinogen and triglyceride levels</p>	<p>Anticytokine therapy recommended^c If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy.</p> <p>Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)</p>	<p>Dexamethasone (eg, 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day.</p>

Abbreviations: CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; IL=interleukin; IV=intravenous(ly); MAS/HLH=macrophage activation syndrome/hemophagocytic lymphohistiocytosis; SC=subcutaneous(ly).

^a Source: (Lee et al., 2019).

^b Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids (Lehmberg et al., 2015).

^c Suggested anticytokine dosing:

- Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg per dose). Repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24-hour period.

- Siltuximab 11 mg/kg IV over 1 hour, 1 time only.
- Anakinra 100 mg SC once/day.
- In more severe CRS cases, especially if combined with MAS/HLH and/or neurotoxicity, anakinra 100-200 mg twice daily (every 12 hours) SC should be given until resolution of CRS and other concurrent T-cell toxicities, like neurotoxicity and/or MAS/HLH which could benefit from anakinra treatment.

10.9 Appendix 9: HLH-2004 Diagnostic Criteria and Management Guidelines

HLH-2004 Diagnostic Criteria

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

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

- 1) Fever
- 2) Splenomegaly
- 3) Cytopenia (affecting ≥ 2 of 3 lineages in peripheral blood)
 - a. Hemoglobin < 90 g/L
 - b. Platelets $< 100 \times 10^9$ /L
 - c. Neutrophils $< 1 \times 10^9$ /L
- 4) Hypertriglyceridemia and/or hypofibrinogenemia
 - a. Fasting triglycerides ≥ 3 mmol/L (ie, ≥ 265 mg/dL)
 - b. Fibrinogen ≤ 1.5 g/L
- 5) Hemophagocytosis in bone marrow or spleen or lymph nodes, no evidence of malignancy
- 6) Low or no NK cell activity
- 7) Ferritin ≥ 500 μ g/L
- 8) Soluble CD25 (ie, IL-2 receptor) ≥ 2400 U/mL

Diagnosis can also be established if molecular diagnosis is consistent with HLH.

HLH Management Guidelines

Supportive care

Early diagnosis and intensive supportive care are essential because of frequent life-threatening, severe manifestations at presentation. Diagnostic workup may include, but is not limited to, specific blood tests in addition to normal hematologic, biochemical, and coagulation profiles (ie, ferritin, fibrinogen, triglyceride level, sCD25, NK cell activity), imaging evaluating for splenomegaly, and bone marrow biopsy if not contraindicated.

Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis, and treatment must be initiated. The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation. Management should be tailored to control hyperinflammation and to treat identified disease triggers.

Upon the first suspicion of the diagnosis, withhold trial treatments and contact the sponsor's medical monitor. A hematology consult may also be considered.

Anticytokine Therapy and Glucocorticoids

First-line treatment: Includes the use of IV steroids, especially in the case of organ-specific irAEs. Pulsed corticosteroids (eg, 1000 mg/day for 3 days according to ([Takahashi et al., 2020](#)))

and elements of the HLH-94 protocol (dexamethasone 10 mg/m² with/without a modified dose of etoposide) may be used. Dose and frequency adjustments are advised for adult patients ([La Rosée et al., 2019](#)). Early intervention with high-dose steroids alone may be successful in the treatment of HLH induced by immune checkpoint blockade ([Sadaat and Jang, 2018](#); [Takahashi et al., 2020](#)).

Alternative/additional regimens could contain IL-6R-blockade with tocilizumab (especially where the event is not improving with steroids within 48-72 hours), unless tocilizumab was already administered for the management of CRS. Additionally, anakinra and IV immune globulin beyond corticosteroids could be used. There are also reports that JAK1/2 inhibitors may be a safe and effective therapy for HLH ([Keenan et al., 2021](#)).

Second-line treatment: Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids. Anakinra should be given until resolution of CRS with a daily dose of 100 mg SC.

In more severe MAS/HLH cases, especially if combined with CRS and/or neurotoxicity, anakinra 100-200 mg SC twice daily (every 12 hours), or higher doses (up to 8 mg/kg/day) in severe cases, should be given until resolution of CRS and other concurrent T-cell toxicities, like neurotoxicity and/or MAS/HLH which could benefit from anakinra treatment.

In case of rapidly progressing clinical course with ongoing CRS, anakinra should be administered as first-line treatment.

11 LAY PROTOCOL SYNOPSIS

NOTE: The lay protocol synopsis supports public disclosure activities and is not meant for site/investigator use.

Protocol Title	A Phase 1 Dose Finding and Phase 2 Randomized, Open-Label Trial to Evaluate the Safety and Clinical Activity of Immunoradiotherapy Combinations as a Treatment Option for Subjects With Metastatic Solid Tumors	
Brief Title	A Safety and Antitumor Activity Trial of Immunoradiotherapy Combinations as a Treatment Option for Subjects with Metastatic Solid Tumors	
Protocol Number	GCT1042-02	
Compound	GEN1042	
Regulatory Agency Identifier Number(s)	EU CT No.	2023-508529-29
	NCT No.	NCT05491317
<p>Brief Summary</p> <p>The goal of this clinical study is to learn about the antibody GEN1042 when it is used alone or used together with another antibody cancer drug, pembrolizumab, after irradiating the tumor directly, for treatment of patients with certain types of cancer.</p> <p>This study has 2 parts. The purpose of the first part is to find out if GEN1042 is safe and to find out the best dose of GEN1042 to use with or without pembrolizumab, after radiation. The purpose of the second part is to give GEN1042 with or without pembrolizumab, after radiation, to more patients to see how well the treatment works against the cancer.</p> <p>All participants who start any part of the study will first receive radiation. Then participants will receive either GEN1042 alone, or GEN1042 with pembrolizumab. These drugs will be administered into the vein. All participants will receive active drug; no one will receive placebo.</p> <p>Part 1 consists of 2 groups. In group 1, participants will receive radiation at a dose of 27 Gy (a dose of 25 Gy may be used instead) followed by GEN1042. After determining a safe dose of GEN1042 to use following radiation treatment, participants in group 2 will also receive pembrolizumab following GEN1042 and radiation treatment.</p> <p>If part 2 should be started, participants will receive radiation and GEN1042, either alone or with pembrolizumab.</p> <p>Participation in the study will require visits to the site. At first there will be weekly visits; after that, visits will lessen over time until they are once every 3 weeks. At site visits, there will be various tests (such as blood draws) and procedures (such as imaging) to monitor whether the treatment is safe and effective. The study duration (including screening, treatment, and follow-up) for each participant will be about 2 years. The treatment duration will be about 18 weeks.</p>		
<p>Rationale</p> <p>GEN1042, also known as DuoBody®-CD40x4-1BB, is an antibody that binds to proteins on cells to help stimulate the body to fight against cancer cells (this type of treatment is known as "immunotherapy"). GEN1042 has been investigated in other clinical studies in different solid tumors but it is not yet approved for treatment of cancer. Another type of immunotherapy treatment known as a checkpoint inhibitor, such as pembrolizumab, has been approved as treatment for patients with certain types of cancer.</p> <p>In addition, animal studies have shown that a combination of GEN1042 with immunotherapy may increase the total effect on the tumor, more than the individual single treatment effect. Treating cancer with radiation prior to treatment with GEN1042 and immunotherapy may also lead to a greater immune response against the cancer.</p>		

Objectives (Purpose) / Endpoints (Assessments)	
<i>Primary Objective(s)</i>	<i>Primary Endpoint(s)</i>
Part 1: Determine the dose of GEN1042 to be given alone or with pembrolizumab following radiation treatment	<ul style="list-style-type: none"> Part 1: How often "dose-limiting toxicities" occur, which are a specific type of side effects that guide the investigators about what doses to test next
Part 2: Evaluate the abscopal response (shrinkage of tumors in parts of the body that were not a direct target of radiation treatment) after treatment with GEN1042 given alone or in combination with pembrolizumab after radiation treatment	<ul style="list-style-type: none"> Part 2: Abscopal response (how tumors that did not receive radiation treatment have reacted [shrinkage, growth, or no change])
<i>Secondary Objective(s)</i>	<i>Secondary Endpoints(s)</i>
Evaluate the ability of GEN1042, given alone or with pembrolizumab, after radiation treatment, to slow or stop tumor growth, or reduce tumor size	<p>The secondary study endpoints are additional ways of measuring a tumor's response to treatment (these will be measured throughout the study):</p> <ul style="list-style-type: none"> Objective response rate (a measurement of how the tumor has reacted [shrinkage or growth] to treatment). This endpoint will be measured on scans done throughout the study both in tumor lesions that received radiation treatment and those that did not. Duration of response (the time period from tumor shrinkage until the growth starts again) Disease control rate (the percentage of participants who obtained either tumor shrinkage or stop of tumor growth during treatment) Progression-free survival (the duration of time during and after treatment that a participant lives with the disease but the cancer does not grow or spread) One-year overall survival (the percentage of patients alive at 1 year after start of treatment with GEN1042 given alone or with pembrolizumab after radiation treatment) Abscopal response (how tumors that did not receive radiation treatment have reacted [gotten smaller or gotten larger])
Measure and assess the types and frequency of side effects and tolerability of GEN1042 when given alone or with pembrolizumab after radiation treatment	<ul style="list-style-type: none"> How often side effects occur and how serious they are, and how often laboratory values are outside the normal range and by how much
Describe the amount of GEN1042 and its removal from blood and the degree of GEN1042 interaction with the body's immune cells	<ul style="list-style-type: none"> Amount of GEN1042 in the blood and how the amount changes over time Measure any unwanted immune reaction against GEN1042
Trial Population Patients 18 years of age or older with cancer (colon cancer, lung cancer, breast cancer, head and neck cancer, prostate cancer, or cancer of the pancreas [organ that makes insulin], esophagus or anus [parts of the digestive tract], or cervix [the lower part of the womb]) that has spread. Patients who are not good candidates for receiving radiation treatment or who already received radiation treatment within 14 days of the start of the radiation treatment in this study are not allowed to participate in this study.	
Ethical Considerations Research in cells, animals, and early information based on this trial suggests that GEN1042 may be effective in treating cancer in humans and may also work together with other cancer drugs, such as pembrolizumab. Pembrolizumab is approved for the treatment of patients with various cancer types.	

Being treated with GEN1042 alone or together with another antibody cancer drug, pembrolizumab, after radiation in this trial may or may not make the health better for an individual subject. Although the health of one participant may not get better, other patients may benefit from the knowledge gained from this study in the future. Participants' health will be observed and monitored during the trial and all tests and procedures performed throughout the trial are done to find out if GEN1042 given alone or given with pembrolizumab is both safe and effective (that is, the drugs can fight cancer). So far, the benefit-risk balance of early studies was positive and warrants further development of GEN1042.

12 REFERENCES

- Ahn, E., Araki, K., Hashimoto, M., Li, W., Riley, J. L., Cheung, J., Sharpe, A. H., Freeman, G. J., Irving, B. A., and Ahmed, R. (2018). Role of PD-1 during effector CD8 T cell differentiation. *Proc Natl Acad Sci U S A* 115, 4749-4754.
- Amin, M. B., Greene, F. L., Edge, S. B., Compton, C. C., Gershengwald, J. E., Brookland, R. K., Meyer, L., Gress, D. M., Byrd, D. R., and Winchester, D. P. (2017). The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin* 67, 93-99.
- Anscher, M. S., Arora, S., Weinstock, C., Amatya, A., Bandaru, P., Tang, C., Girvin, A. T., Fiero, M. H., Tang, S., Lubitz, R., *et al.* (2022). Association of Radiation Therapy With Risk of Adverse Events in Patients Receiving Immunotherapy: A Pooled Analysis of Trials in the US Food and Drug Administration Database. *JAMA Oncol.*
- Antonia, S. J., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R., Kurata, T., Chiappori, A., Lee, K. H., de Wit, M., *et al.* (2018). Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med* 379, 2342-2350.
- Battisti, W. P., Wager, E., Baltzer, L., Bridges, D., Cairns, A., Carswell, C. I., Citrome, L., Gurr, J. A., Mooney, L. A., Moore, B. J., *et al.* (2015). Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. *Ann Intern Med* 163, 461-464.
- Bavencio SmPC (2020). Bavencio Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information_en.pdf. Accessed March 2022.
- Brooks, E. D., and Chang, J. Y. (2019). Time to abandon single-site irradiation for inducing abscopal effects. *Nat Rev Clin Oncol* 16, 123-135.
- Buchwald, Z. S., Wynne, J., Nasti, T. H., Zhu, S., Mourad, W. F., Yan, W., Gupta, S., Khleif, S. N., and Khan, M. K. (2018). Radiation, Immune Checkpoint Blockade and the Abscopal Effect: A Critical Review on Timing, Dose and Fractionation. *Front Oncol* 8, 612.
- Craig, D. J., Nanavaty, N. S., Devanaboyina, M., Stanbery, L., Hamouda, D., Edelman, G., Dworkin, L., and Nemunaitis, J. J. (2021). The abscopal effect of radiation therapy. *Future Oncol* 17, 1683-1694.
- CTFG (2020). Clinical Trial Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials, version 1.1. CTFG 21/09/2020. Available from: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf.
- Deng, L., Liang, H., Burnette, B., Beckett, M., Darga, T., Weichselbaum, R. R., and Fu, Y. X. (2014). Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* 124, 687-695.

Derer, A., Spiljar, M., Bäumler, M., Hecht, M., Fietkau, R., Frey, B., and Gaipl, U. S. (2016). Chemoradiation Increases PD-L1 Expression in Certain Melanoma and Glioblastoma Cells. *Front Immunol* 7, 610.

Dewan, M. Z., Galloway, A. E., Kawashima, N., Dewyngaert, J. K., Babb, J. S., Formenti, S. C., and Demaria, S. (2009). Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res* 15, 5379-5388.

Dovedi, S. J., Adlard, A. L., Lipowska-Bhalla, G., McKenna, C., Jones, S., Cheadle, E. J., Stratford, I. J., Poon, E., Morrow, M., Stewart, R., *et al.* (2014). Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res* 74, 5458-5468.

Eggermont, A. M., Chiarion-Sileni, V., Grob, J. J., Dummer, R., Wolchok, J. D., Schmidt, H., Hamid, O., Robert, C., Ascierto, P. A., Richards, J. M., *et al.* (2016). Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. *N Engl J Med* 375, 1845-1855.

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., *et al.* (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45, 228-247.

FDA (2009). Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

Foster, C. C., Pitroda, S. P., and Weichselbaum, R. R. (2020). Definition, Biology, and History of Oligometastatic and Oligoprogressive Disease. *Cancer J* 26, 96-99.

Frey, B., Rückert, M., Weber, J., Mayr, X., Derer, A., Lotter, M., Bert, C., Rödel, F., Fietkau, R., and Gaipl, U. S. (2017). Hypofractionated Irradiation Has Immune Stimulatory Potential and Induces a Timely Restricted Infiltration of Immune Cells in Colon Cancer Tumors. *Front Immunol* 8, 231.

Gomez, D. R., Tang, C., Zhang, J., Blumenschein, G. R., Jr., Hernandez, M., Lee, J. J., Ye, R., Palma, D. A., Louie, A. V., Camidge, D. R., *et al.* (2019). Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J Clin Oncol* 37, 1558-1565.

Gray, J. E., Villegas, A., Daniel, D., Vicente, D., Murakami, S., Hui, R., Kurata, T., Chiappori, A., Lee, K. H., Cho, B. C., *et al.* (2020). Three-Year Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC-Update from PACIFIC. *J Thorac Oncol* 15, 288-293.

Grills, I. S., Mangona, V. S., Welsh, R., Chmielewski, G., McInerney, E., Martin, S., Wloch, J., Ye, H., and Kestin, L. L. (2010). Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol* 28, 928-935.

Guckenberger, M., Andratschke, N., Alheit, H., Holy, R., Moustakis, C., Nestle, U., and Sauer, O. (2014). Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. *Strahlenther Onkol* 190, 26-33.

Guerrero, M., and Li, X. A. (2004). Extending the linear-quadratic model for large fraction doses pertinent to stereotactic radiotherapy. *Phys Med Biol* 49, 4825-4835.

Hellman, S., and Weichselbaum, R. R. (1995). Oligometastases. *J Clin Oncol* 13, 8-10.

Hettich, M., Lahoti, J., Prasad, S., and Niedermann, G. (2016). Checkpoint Antibodies but not T Cell-Recruiting Diabodies Effectively Synergize with TIL-Inducing γ -Irradiation. *Cancer Res* 76, 4673-4683.

Hutchinson, K. E., Yost, S. E., Chang, C. W., Johnson, R. M., Carr, A. R., McAdam, P. R., Halligan, D. L., Chang, C. C., Schmolze, D., Liang, J., and Yuan, Y. (2020). Comprehensive Profiling of Poor-Risk Paired Primary and Recurrent Triple-Negative Breast Cancers Reveals Immune Phenotype Shifts. *Clin Cancer Res* 26, 657-668.

Hwang, W. L., Pike, L. R. G., Royce, T. J., Mahal, B. A., and Loeffler, J. S. (2018). Safety of combining radiotherapy with immune-checkpoint inhibition. *Nat Rev Clin Oncol* 15, 477-494.

ICMJE (2010). Uniform requirements for manuscripts submitted to biomedical journals: Writing and editing for biomedical publication. *J Pharmacol Pharmacother* 1, 42-58.

ICMJE (2016). Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated December 2016. Available at: <http://www.icmje.org/recommendations/>.

ICMJE (2019). Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Updated December 2019. Available at: <http://www.icmje.org/recommendations/>.

Imfinzi SmPC Imfinzi Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf. Accessed January 2022.

Iyengar, P., Wardak, Z., Gerber, D. E., Tumati, V., Ahn, C., Hughes, R. S., Dowell, J. E., Cheedella, N., Nedzi, L., Westover, K. D., *et al.* (2018). Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol* 4, e173501.

Jagodinsky, J. C., Harari, P. M., and Morris, Z. S. (2020). The Promise of Combining Radiation Therapy With Immunotherapy. *Int J Radiat Oncol Biol Phys* 108, 6-16.

Johnson, M., Lopez, J., LoRusso, P., Bauman, J., Haggstrom, D., Lagkadinou, E., Bajaj, G., Türeci, Ö., Adams, H., Şahin, U., *et al.* (2021). 493 First-in-human phase 1/2 trial to evaluate the safety and initial clinical activity of DuoBody®-CD40 $\times$ 4-1BB (GEN1042) in patients with advanced solid tumors. *J Immunother Cancer* 9, A525-A525.

Joseph, R. W., Elassaiss-Schaap, J., Kefford, R., Hwu, W. J., Wolchok, J. D., Joshua, A. M., Ribas, A., Hodi, F. S., Hamid, O., Robert, C., *et al.* (2018). Baseline Tumor Size Is an Independent Prognostic Factor for Overall Survival in Patients with Melanoma Treated with Pembrolizumab. *Clin Cancer Res* 24, 4960-4967.

Keenan, C., Nichols, K. E., and Albeituni, S. (2021). Use of the JAK Inhibitor Ruxolitinib in the Treatment of Hemophagocytic Lymphohistiocytosis. *Front Immunol* *12*, 614704.

Kelly, R. J., Ajani, J. A., Kuzdzal, J., Zander, T., Van Cutsem, E., Piessen, G., Mendez, G., Feliciano, J., Motoyama, S., Lièvre, A., *et al.* (2021). Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med* *384*, 1191-1203.

Keytruda SmPC (2020). Keytruda Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf. Accessed November 2021.

Kim, S. H., Park, S. Y., Lim, M. C., Lee, E. S., Lee, E. G., Han, S. E., Kim, Y. H., Kwon, B. S., and Choi, B. K. (2019). Delayed IL-21 treatment preferentially expands peptide-specific CD8(+) T cells by reducing bystander activation of T cells. *Immunotherapy* *11*, 497-513.

Kulzer, L., Rubner, Y., Deloch, L., Allgäuer, A., Frey, B., Fietkau, R., Dörrie, J., Schaft, N., and Gaip, U. S. (2014). Norm- and hypo-fractionated radiotherapy is capable of activating human dendritic cells. *J Immunotoxicol* *11*, 328-336.

La Rosée, P., Horne, A., Hines, M., von Bahr Greenwood, T., Machowicz, R., Berliner, N., Birndt, S., Gil-Herrera, J., Girschikofsky, M., Jordan, M. B., *et al.* (2019). Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood* *133*, 2465-2477.

Le Tourneau, C., Lee, J. J., and Siu, L. L. (2009). Dose escalation methods in phase I cancer clinical trials. *J Natl Cancer Inst* *101*, 708-720.

Lee, D. W., Santomasso, B. D., Locke, F. L., Ghobadi, A., Turtle, C. J., Brudno, J. N., Maus, M. V., Park, J. H., Mead, E., Pavletic, S., *et al.* (2019). ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* *25*, 625-638.

Lehmberg, K., Nichols, K. E., Henter, J. I., Girschikofsky, M., Greenwood, T., Jordan, M., Kumar, A., Minkov, M., La Rosée, P., and Weitzman, S. (2015). Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. *Haematologica* *100*, 997-1004.

Lievens, Y., Guckenberger, M., Gomez, D., Hoyer, M., Iyengar, P., Kindts, I., Méndez Romero, A., Nevens, D., Palma, D., Park, C., *et al.* (2020). Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol* *148*, 157-166.

Lugade, A. A., Moran, J. P., Gerber, S. A., Rose, R. C., Frelinger, J. G., and Lord, E. M. (2005). Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol* *174*, 7516-7523.

Maity, A., Mick, R., Huang, A. C., George, S. M., Farwell, M. D., Lukens, J. N., Berman, A. T., Mitchell, T. C., Bauml, J., Schuchter, L. M., *et al.* (2018). A phase I trial of pembrolizumab with hypofractionated radiotherapy in patients with metastatic solid tumours. *Br J Cancer* *119*, 1200-1207.

Masini, C., Iotti, C., De Giorgi, U., Bellia, R. S., Buti, S., Salaroli, F., Zampiva, I., Mazzarotto, R., Mucciarini, C., Vitale, M. G., *et al.* (2022). Nivolumab in Combination with Stereotactic Body Radiotherapy in Pretreated Patients with Metastatic Renal Cell Carcinoma. Results of the Phase II NIVES Study. *Eur Urol* 81, 274-282.

McBride, S., Sherman, E., Tsai, C. J., Baxi, S., Aghalar, J., Eng, J., Zhi, W. I., McFarland, D., Michel, L. S., Young, R., *et al.* (2021). Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma. *J Clin Oncol* 39, 30-37.

NCI (2020). Off Target: Investigating the Abscopal Effect as a Treatment for Cancer. Available at: <https://www.cancer.gov/news-events/cancer-currents-blog/2020/cancer-abscopal-effect-radiation-immunotherapy>. Accessed November 2021.

Nikanjam, M., Patel, H., and Kurzrock, R. (2017). Dosing immunotherapy combinations: Analysis of 3,526 patients for toxicity and response patterns. *Oncoimmunology* 6, e1338997.

Opdivo SmPC Opdivo Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf. Accessed January 2022.

Ost, P., Reynders, D., Decaestecker, K., Fonteyne, V., Lumen, N., De Bruycker, A., Lambert, B., Delrue, L., Bultijnck, R., Claeys, T., *et al.* (2018). Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol* 36, 446-453.

Palma, D., Visser, O., Lagerwaard, F. J., Belderbos, J., Slotman, B. J., and Senan, S. (2010). Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 28, 5153-5159.

Palma, D. A., Olson, R., Harrow, S., Gaede, S., Louie, A. V., Haasbeek, C., Mulroy, L., Lock, M., Rodrigues, G. B., Yaremko, B. P., *et al.* (2019). Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 393, 2051-2058.

Palma, D. A., Salama, J. K., Lo, S. S., Senan, S., Treasure, T., Govindan, R., and Weichselbaum, R. (2014). The oligometastatic state - separating truth from wishful thinking. *Nat Rev Clin Oncol* 11, 549-557.

Phillips, R., Shi, W. Y., Deek, M., Radwan, N., Lim, S. J., Antonarakis, E. S., Rowe, S. P., Ross, A. E., Gorin, M. A., Deville, C., *et al.* (2020). Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol* 6, 650-659.

Pollom, E. L., Chin, A. L., Diehn, M., Loo, B. W., and Chang, D. T. (2017). Normal Tissue Constraints for Abdominal and Thoracic Stereotactic Body Radiotherapy. *Semin Radiat Oncol* 27, 197-208.

Postow, M. A., Callahan, M. K., Barker, C. A., Yamada, Y., Yuan, J., Kitano, S., Mu, Z., Rasalan, T., Adamow, M., Ritter, E., *et al.* (2012). Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* 366, 925-931.

Rech, A. J., Dada, H., Kotzin, J. J., Henao-Mejia, J., Minn, A. J., Twyman-Saint Victor, C., and Vonderheide, R. H. (2018). Radiotherapy and CD40 Activation Separately Augment Immunity to Checkpoint Blockade in Cancer. *Cancer Res* 78, 4282-4291.

Rogatko, A., Schoeneck, D., Jonas, W., Tighiouart, M., Khuri, F. R., and Porter, A. (2007). Translation of innovative designs into phase I trials. *J Clin Oncol* 25, 4982-4986.

Sadaat, M., and Jang, S. (2018). Hemophagocytic lymphohistiocytosis with immunotherapy: brief review and case report. *J Immunother Cancer* 6, 49.

Sagiv-Barfi, I., Rajapaksa, A., Czerwinski, D., Chang, S., Hebb, J., Chester, C., Waller, E., Fine, G., Chen, D., Kowanetz, M., *et al.* (2014). Abstract 2941: Local tumor irradiation combined with α -PDL-1 immune checkpoint inhibition results in local and systemic anti-tumor responses: Successful translation of a mouse model to a human case series. *Cancer Research* 74, 2941-2941.

Salama, J. K., and Milano, M. T. (2014). Radical irradiation of extracranial oligometastases. *J Clin Oncol* 32, 2902-2912.

Schaue, D., Ratikan, J. A., Iwamoto, K. S., and McBride, W. H. (2012). Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys* 83, 1306-1310.

Schneider, B. J., Naidoo, J., Santomasso, B. D., Lacchetti, C., Adkins, S., Anadkat, M., Atkins, M. B., Brassil, K. J., Caterino, J. M., Chau, I., *et al.* (2021). Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. *J Clin Oncol* 39, 4073-4126.

Schoenfeld, J. D., Giobbie-Hurder, A., Ranasinghe, S., Kao, K. Z., Lako, A., Tsuji, J., Liu, Y., Brennick, R. C., Gentzler, R. D., Lee, C., *et al.* (2022). Durvalumab plus tremelimumab alone or in combination with low-dose or hypofractionated radiotherapy in metastatic non-small-cell lung cancer refractory to previous PD(L)-1 therapy: an open-label, multicentre, randomised, phase 2 trial. *Lancet Oncol* 23, 279-291.

Seymour, L., Bogaerts, J., Perrone, A., Ford, R., Schwartz, L. H., Mandrekar, S., Lin, N. U., Litieri, S., Dancey, J., Chen, A., *et al.* (2017). iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 18, e143-e152.

Shaverdian, N., Lisberg, A. E., Bornazyan, K., Veruttipong, D., Goldman, J. W., Formenti, S. C., Garon, E. B., and Lee, P. (2017). Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* 18, 895-903.

Spaas, M., Sundahl, N., Kruse, V., Rottey, S., De Maeseneer, D., Duprez, F., Lievens, Y., Surmont, V., Brochez, L., Reynders, D., *et al.* (2023). Checkpoint Inhibitors in Combination With Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors: The CHEERS Phase 2 Randomized Clinical Trial. *JAMA Oncol* 9, 1205-1213.

Stone, H. B., Peters, L. J., and Milas, L. (1979). Effect of host immune capability on radiocurability and subsequent transplantability of a murine fibrosarcoma. *J Natl Cancer Inst* 63, 1229-1235.

Takahashi, H., Koiwa, T., Fujita, A., Suzuki, T., Tagashira, A., and Iwasaki, Y. (2020). A case of pembrolizumab-induced hemophagocytic lymphohistiocytosis successfully treated with pulse glucocorticoid therapy. *Respir Med Case Rep* 30, 101097.

Tang, C., Welsh, J. W., de Groot, P., Massarelli, E., Chang, J. Y., Hess, K. R., Basu, S., Curran, M. A., Cabanillas, M. E., Subbiah, V., *et al.* (2017). Ipilimumab with Stereotactic Ablative Radiation Therapy: Phase I Results and Immunologic Correlates from Peripheral T Cells. *Clin Cancer Res* 23, 1388-1396.

Tecentriq SmPC Tecentriq Summary of Product Characteristics. Available at: https://www.ema.europa.eu/documents/product-information/tecentriq-epar-product-information_en.pdf. September 2018.

Theelen, W., Peulen, H. M. U., Lalezari, F., van der Noort, V., de Vries, J. F., Aerts, J., Dumoulin, D. W., Bahce, I., Niemeijer, A. N., de Langen, A. J., *et al.* (2019). Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. *JAMA Oncol* 5, 1276-1282.

Turchan, W. T., Pitroda, S. P., and Weichselbaum, R. R. (2021). Radiotherapy and Immunotherapy Combinations in the Treatment of Patients with Metastatic Disease: Current Status and Future Focus. *Clin Cancer Res* 27, 5188-5194.

Welsh, J., Menon, H., Chen, D., Verma, V., Tang, C., Altan, M., Hess, K., de Groot, P., Nguyen, Q. N., Varghese, R., *et al.* (2020). Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial. *J Immunother Cancer* 8.

Yervoy SmPC (2016). Yervoy Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/yervoy-epar-product-information_en.pdf. Accessed March 2022.

Yu, J., Green, M. D., Li, S., Sun, Y., Journey, S. N., Choi, J. E., Rizvi, S. M., Qin, A., Waninger, J. J., Lang, X., *et al.* (2021). Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med* 27, 152-164.

Zhao, X., and Shao, C. (2020). Radiotherapy-Mediated Immunomodulation and Anti-Tumor Abscopal Effect Combining Immune Checkpoint Blockade. *Cancers (Basel)* 12.

Zhou, X., Ramachandran, S., Mann, M., and Popkin, D. L. (2012). Role of lymphocytic choriomeningitis virus (LCMV) in understanding viral immunology: past, present and future. *Viruses* 4, 2650-2669.

Zimmer, L., Livingstone, E., Hassel, J. C., Fluck, M., Eigentler, T., Loquai, C., Haferkamp, S., Gutzmer, R., Meier, F., Mohr, P., *et al.* (2020). Adjuvant nivolumab plus ipilimumab or nivolumab monotherapy versus placebo in patients with resected stage IV melanoma with no

evidence of disease (IMMUNED): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 395, 1558-1568.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure that they are fully informed regarding the trial drug, the conduct of the trial, and the obligations of confidentiality.

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

Coordinating Investigator (where required):

Name (typed or printed):

Institution and Address:

Signature:

Date:

(dd-Mmm-yyyy)

Principal (Site) Investigator:

Name (typed or printed):

Institution and Address:

Telephone Number:

Signature:

Date:

(dd-Mmm-yyyy)