CLINICAL TRIAL PROTOCOL

Protocol Title	Efficacy and Safety Study of Acasunlimab as Monotherapy and in Combination With Pembrolizumab in Subjects With Relapsed/Refractory, Unresectable Locally Advanced or Metastatic Cutaneous Melanoma That Progressed On or After Treatment With a Checkpoint Inhibitor		
Protocol Number	GCT1046-07		
Compound	Acasunlimab (GEN1046; DuoBody®-PD-L1x4-1BB)		
Brief Title	Study of the Effectiveness and Safety of Acasunlimab Alone or With Pembrolizumab in Treating Advanced Melanoma of the Skin That Returned After or Did Not Respond to Checkpoint Inhibitor Therapy		
Trial Phase	2		
Sponsor Name	Genmab*		
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	Title	PPD	
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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 for all other countries	Genmab US, Inc. 777 Scudders Mill Rd Plainsboro, New Jersey 08536 United States of America

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

INVESTIGATOR AGREEMENT

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

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

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

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

Signature: _____ Date: _____
(DD Mmm YYYY)

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

Coordinating Investigator (Where Required):	
Name (typed or printed):	
Institution and Address:	

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

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

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LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	first-line
2L	second-line
ADA	antidrug antibody
ADAS	anti-drug antibody analysis set
ADL	activities of daily living
AE	adverse event
ALT	alanine transaminase
AHA	American Heart Association
AJCC	American Joint Committee on Cancer
AMP	auxiliary medicinal product
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
aPTT	activated partial thromboplastin time
ASAP	as soon as possible
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
ASTCT	American Society for Transplantation and Cellular Therapy
BiPAP	bilevel positive airway pressure
BOR	best overall response
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BUN	blood urea nitrogen
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T-cell
CD	cluster of differentiation
cfDNA	cell-free deoxyribonucleic acid
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
COA	clinical outcome assessment
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure

Abbreviation	Definition
CPI	checkpoint inhibitor
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine release syndrome
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trials Facilitation Group
CTIS	Clinical Trials Information System
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTLS	clinical tumor lysis syndrome
CxDx	cycle X day X
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram
EOI	end of infusion
EOT	end of treatment
ePRO	electronic patient-reported outcomes
EU	European Union
FACT-GP5	Functional Assessment of Cancer Therapy-General item GP5
FACT-M	Functional Assessment of Cancer Therapy–Melanoma
FAS	full analysis set
Fc	crystallizable fragment
FcγR	Fc gamma receptor
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FIH	first in human
FSH	follicle-stimulating hormone

Abbreviation	Definition
FU	follow up
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GDPR	General Data Protection Regulation
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HbA1C	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLH	hemophagocytic lymphohistiocytosis
IB	investigator's brochure
ICANS	immune effector cell-associated neurotoxicity syndrome
ICE	immune effector cell-associated encephalopathy
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP	intracranial pressure
IEC	independent ethics committee
IFN	interferon
IFNγ	interferon gamma
Ig	immunoglobulin
IgG	immunoglobulin G
IHC	immunohistochemistry
IIV	interindividual variability
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
irAE	immune-related adverse event
IRB	institutional review board

Abbreviation	Definition
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous(ly)
JAK	Janus kinase
LAG-3	lymphocyte activation gene 3
LDH	lactate dehydrogenase
LFT	liver function test
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MAS	macrophage activation syndrome
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MEK	mitogen-activated protein kinase kinase
MMR	measles, mumps, and rubella
MoA	mechanism of action
MRI	magnetic resonance imaging
NaF	sodium fluoride
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NK	natural killer
NOAEL	no-observed-adverse-effect level
NR	not reached
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell(s)
PCR	polymerase chain reaction
PD	progressive disease/disease progression
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2

Abbreviation	Definition
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PKS	pharmacokinetics analysis set
PO	orally
PPoS	predictive probability of success
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q12W	every 12 weeks
QA	quality assurance
QW	every week/once a week/weekly
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RSV	respiratory syncytial virus
RZV	recombinant zoster vaccine
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SAS	safety analysis set
SC	subcutaneous
SD	stable disease
SFU	safety follow up
SmPC	Summary of Product Characteristics
SOC	standard of care
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
Tdap	tetanus, diphtheria, and acellular pertussis
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TIGIT	T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif domains
TIL	tumor-infiltrating lymphocytes
TIM3	T-cell immunoglobulin and mucin domain-containing protein 3
TLS	tumor lysis syndrome
TMB	tumor mutational burden
TNBC	triple negative breast cancer
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of normal
UNS	unscheduled
US	United States
USA	United States of America
USPI	United States prescribing information
WBC	white blood cell(s)
WNL	within normal limits

1 PROTOCOL SUMMARY

1.1 Trial Synopsis

Protocol Title:	Efficacy and Safety Study of Acasunlimab as Monotherapy and in Combination With Pembrolizumab in Subjects With Relapsed/Refractory, Unresectable Locally Advanced or Metastatic Cutaneous Melanoma That Progressed On or After Treatment With a Checkpoint Inhibitor
Brief Title:	Study of the Effectiveness and Safety of Acasunlimab Alone or With Pembrolizumab in Treating Advanced Melanoma of the Skin That Returned After or Did Not Respond to Checkpoint Inhibitor Therapy
Trial Phase:	2
Indication:	Relapsed/Refractory, Locally Advanced or Metastatic Cutaneous Melanoma

Rationale:

There is an unmet medical need for novel treatment modalities that improve response rates and survival in patients with advanced unresectable cutaneous melanoma, regardless of BRAF mutation status, who progressed on or after checkpoint inhibitor (CPI) therapy.

Acasunlimab (GEN1046; DuoBody®-PD-L1×4-1BB) is a bispecific antibody targeting programmed death ligand 1 (PD-L1) and 4-1BB that induces activation of T cells by simultaneously blocking an inhibitory signal via the programmed cell death protein 1 (PD-1)/PD-L1 axis and conditionally inducing a stimulatory signal via 4-1BB.

In the first-in-human clinical trial GCT1046-01, confirmed objective responses were observed with acasunlimab monotherapy in a PD-L1 unselected, heavily pretreated population of subjects with non-small cell lung cancer (NSCLC) who were previously treated with a PD-1/PD-L1 inhibitor. Additionally, in the Phase 2 trial GCT1046-04, the combination of acasunlimab with the PD-1 inhibitor pembrolizumab administered every 6 weeks (Q6W) improved durability of responses and overall survival (OS) versus acasunlimab monotherapy and acasunlimab plus pembrolizumab administered every 3 weeks (Q3W) in subjects with PD-L1+ metastatic NSCLC. The safety profile of acasunlimab monotherapy and acasunlimab in combination with pembrolizumab was manageable.

The purpose of this trial is to investigate the efficacy and safety of acasunlimab as monotherapy and in combination with pembrolizumab in adult subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma (BRAF wild type or mutant) that progressed on or after treatment with CPI therapy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Evaluate the antitumor activity of acasunlimab as monotherapy and in combination with pembrolizumab.	Objective response rate (ORR) assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary	
Evaluate the time to onset and durability of the antitumor response of acasunlimab as monotherapy and in combination with pembrolizumab.	• Time to response (TTR) assessed by the investigator per RECIST v1.1 • Duration of response (DOR) assessed by the investigator per RECIST v1.1
Evaluate progression-free survival (PFS) and OS in subjects treated with acasunlimab as monotherapy and in combination with pembrolizumab.	• PFS assessed by the investigator per RECIST v1.1 • OS
Assess the safety and tolerability of acasunlimab as monotherapy and in combination with pembrolizumab.	• Occurrence and severity of adverse events (AE) • Time to treatment discontinuation due to AE

Trial Design and Duration:

This is a Phase 2, randomized, open-label, multicenter trial evaluating the efficacy and safety of acasunlimab as monotherapy and in combination with pembrolizumab in adult subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma that progressed on or after prior CPI-containing therapy.

Subjects will be randomized 1:1 to receive either:

- Acasunlimab 100 mg Q6W + pembrolizumab 400 mg Q6W (Arm A)
- Acasunlimab 100 mg Q6W (Arm B)

The randomization will be stratified by:

- BRAF V600 mutational status: wild type vs mutant
- Lactate dehydrogenase levels: ≤ upper limit of normal (ULN) vs > ULN

Treatment should continue until a subject experiences disease progression or unacceptable AEs requiring treatment discontinuation. Subjects who discontinue from the trial will not be replaced. Crossover is not allowed within this trial. However, treatment beyond progression with acasunlimab in combination with pembrolizumab may be allowed on an individual basis following discussion with the sponsor. After treatment discontinuation, subjects enter a 90-day safety follow-up period, followed by survival follow-up.

Number of Subjects:

Approximately 90 subjects are planned to be treated in this trial, ie, approximately 45 subjects treated in each arm.

Summary of Key Eligibility Criteria:

Key Inclusion Criteria:

- Subjects ≥ 18 years of age with histologically or cytologically confirmed diagnosis of relapsed/refractory, locally advanced unresectable (Stage IIIB, IIIC, or IIID) or metastatic (Stage IV) cutaneous melanoma, per American Joint Committee on Cancer (8th edition) staging.
- Subject must have radiographic progression based on RECIST v1.1 on or following ≥ 1 prior systemic therapy according to local and international guidelines, including a PD-1 blocking antibody treatment or combination treatment containing a PD-1 blocking antibody for relapsed/refractory, locally advanced unresectable (Stage IIIB, IIIC, or IIID) or metastatic (Stage IV) cutaneous melanoma.
  - Subject must have received a minimum of 2 cycles of an approved PD-1 blocking antibody monotherapy or combination therapy, and a best overall response (BOR) based on RECIST v1.1 of complete response, partial response, or stable disease must be known and documented.
  - Neoadjuvant and/or adjuvant systemic therapy count as the first line of prior systemic therapy if there is documented disease progression ≤ 6 months after completion of therapy.
  - A confirmatory scan is required ≥ 4 weeks after initial evidence of progressive disease following treatment with CPI therapy, provided that the subject is clinically stable prior to Cycle 1 Day 1 in this trial (note: this second confirmatory scan can be performed during the screening period).
- Subjects are eligible regardless of BRAF V600 mutational status (wild type or mutant). BRAF V600 mutational status must be determined by local assessment and documented prior to enrollment.
- Subjects with a BRAF V600 mutation should have received prior BRAF-directed therapy (with or without a MEK inhibitor) prior to enrollment in the trial, unless deemed not clinically indicated by the Investigator due to concurrent medical condition or prior toxicity.
- At least 1 measurable target lesion, as defined by RECIST v1.1
- Subject has an Eastern Cooperative Oncology Group performance status of 0 or 1 within 7 days prior to Cycle 1 Day 1.
- Subject has a life expectancy of ≥ 3 months.

Key Exclusion Criteria:

- Subjects with non-cutaneous or acral melanoma.
- Subject had disease progression as BOR to prior PD-1/PD-L1 containing regimen in the metastatic setting.

- Treatment with an anticancer agent within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of trial treatment.
- Subjects with newly identified or known unstable or symptomatic central nervous system metastases or history of carcinomatous meningitis.

Trial Treatment:

Investigational Medicinal Product(s):

Subjects in Arm A will receive acasunlimab 100 mg in combination with pembrolizumab 400 mg Q6W via intravenous (IV) infusion. Pembrolizumab will be administered first followed by acasunlimab.

Subjects in Arm B will receive acasunlimab 100 mg Q6W via IV infusion.

Auxiliary Medicinal Product(s):

Dexamethasone or methylprednisolone or prednisone (or equivalent) as:

- Reactive steroid premedication recommended to prevent immune-related AEs (irAE) if episodes occurred with previous cycles of trial drug. Suggested dose of prednisone is 10 mg daily (or equivalent) for at least 10 days.
- Management of immune-mediated hepatitis. Initial dose of 0.5-2 mg/kg methylprednisolone or equivalent until Grade ≤ 1

Statistics:

The trial is not designed to detect statistically significant differences between arms.

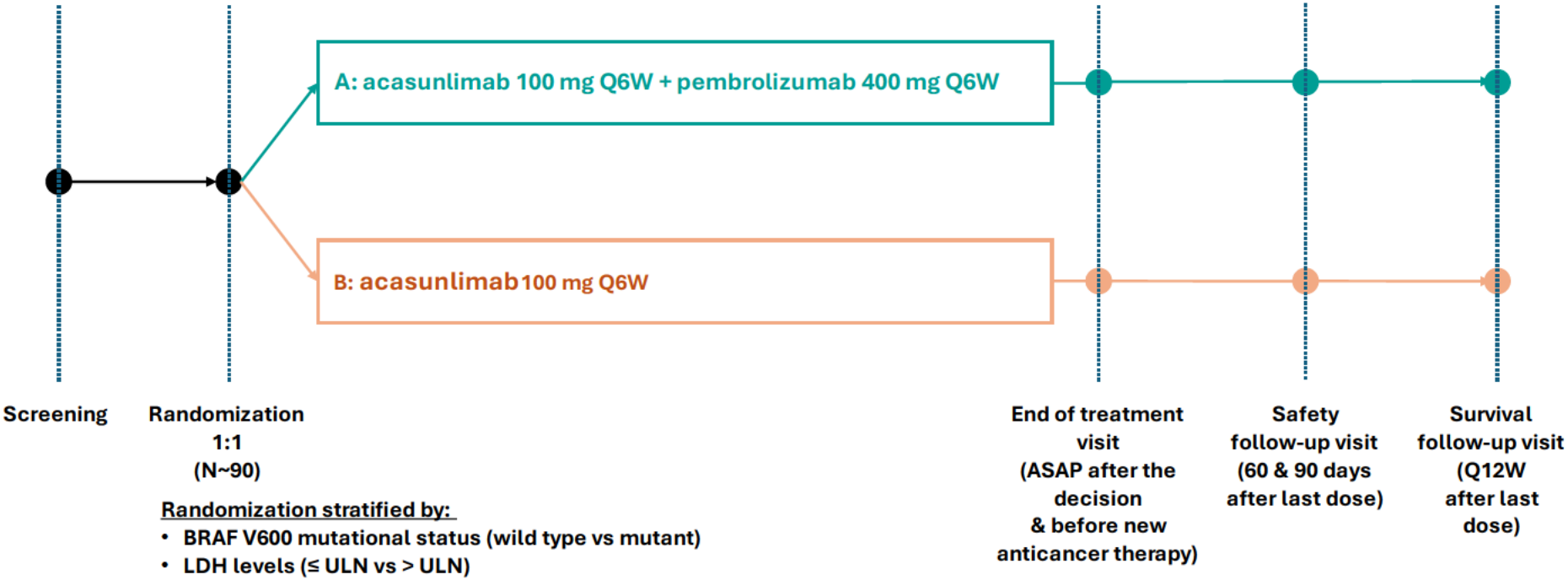
The analysis of ORR as assessed by the investigator per RECIST v1.1 (primary endpoint) and its exact 2-sided 95% confidence interval, using the Clopper-Pearson method, will be presented by treatment arm. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factors, will be used to compare ORR between the 2 treatment arms, at the 1-sided 2.5% level of significance, and the odds ratio will be presented with a 2-sided 95% confidence interval. An interim analysis for futility will be conducted after approximately 20 subjects per arm are evaluable for ORR. The primary analysis of ORR will be conducted approximately 12 months after the last subject's first dose.

Secondary endpoints including TTR, DOR, and PFS as assessed by the investigator per RECIST v1.1, and OS will be summarized by treatment arm using Kaplan-Meier plots and respective medians with 95% confidence intervals will be estimated using the Kaplan-Meier method.

Approximately 90 subjects are expected to be treated in the trial, with approximately 45 subjects treated in each arm. The treatment will be considered promising if the exact 1-sided 95% lower confidence limit for ORR exceeds 20% percent. With 45 subjects per arm and a true ORR of 35% and 40%, the power to meet this criterion is 65% and 86%, respectively. To reject the null hypothesis (ORR = 20%), at least 15 responders out of 45 subjects are required.

1.2 Schema

Figure 1: Trial Schema



Abbreviations: ASAP=as soon as possible; BRAF=B-Raf proto-oncogene, serine/threonine kinase; LDH=lactate dehydrogenase; Q6W=every 6 weeks; Q12W=every 12 weeks.

1.3 Schedule of Activities

Schedule of Activities Tables	
Table 1:	Schedule of Activities (Arm A and Arm B)
Table 2:	Schedule of Biomarker Assessments
Table 3:	Schedule of PK and ADA Sampling

Table 1: Schedule of Activities (Arm A and Arm B)

Period			Screening		Treatment Period (42-Day Cycles)												Post-Treatment Period				UNS
Cycle/Visit	Section	Notes			Cycle 1-2						Cycle 3-4				Cycle 5 Onward[a]		EoT[b]	SFU1	SFU2	Survival FU[c]	
Day			≤28d prior to C1D1	≤7d prior to C1D1	D1	D8	D15	D22	D29	D36	D1	D8	D15	D22	D1	D22	-	60d after last dose	90d after last dose	Q12W after last dose	
Visit window					+3d or ±3d[d]	±2d	±2d	±2d	±2d	±2d	±3d	±2d	±2d	±2d	±3d	±3d		±5d	±7d	±14d	
Informed consent	10.1.6	Must be signed before any trial-related activity.	X																		
Eligibility criteria	5.1, 5.2		X																		
Demographics	8.1.1		X																		
Medical history	8.1.2, 8.1.3	Includes melanoma disease status at initial diagnosis and screening.	X																		
Prior/Concomitant medication	6.6.3		X	X	X[e]	X	X	X	X	X	X[e]	X	X	X	X[e]	X	X	X	X	X		X[f]
COVID-19 and/or influenza infection(s) history[g]	8.1.4		X																		
Prophylactic vaccine history[g,h,i]	6.6.2	Record timing of all prophylactic vaccines received in the last 6 months prior to C1D1.	X																		
COVID-19 booster vaccine[g,i]	6.6.2	Recommended if none administered within the last 2 months	X																		
Prior anticancer therapy/surgery/radiotherapy	6.6.1	Documented since initial diagnosis of melanoma	X																		
Full Physical examination	8.3.1		X		X												X				X[f]
Clinically indicated physical examination	8.3.1					X		X			X[e]	X			X[e]			X			X
Vital signs	8.3.3		X		X[e]	X	X	X	X	X	X[e]	X	X	X	X[e]	X	X	X	X	X		X[f]
Height	8.3.2		X																		
Weight	8.3.2		X		X[e]						X[e]				X[e]		X				X
ECOG PS	8.3.5	Investigator assessed	X		X[e]						X[e]				X[e]		X	X	X		X[f]
On-trial procedures and surgeries	6.6.3.1	C1D1 assessment to be collected after first dose.			X[e]						X[e]				X[e]		X				X[f]

Period			Screening		Treatment Period (42-Day Cycles)												Post-Treatment Period				UNS
Cycle/Visit	Section	Notes			Cycle 1-2						Cycle 3-4				Cycle 5 Onward[a]		EoT[b]	SFU1	SFU2	Survival FU[c]	
Day			≤28d prior to C1D1	≤7d prior to C1D1	D1	D8	D15	D22	D29	D36	D1	D8	D15	D22	D1	D22	-	60d after last dose	90d after last dose	Q12W after last dose	
Visit window					+3d or ±3d[d]	±2d	±2d	±2d	±2d	±2d	±3d	±2d	±2d	±2d	±3d	±3d		±5d	±7d	±14d	
On-trial radiotherapy	6.6.3.1	C1D1 assessment to be collected after first dose.			X[e]	X	X	X	X	X	X[e]	X	X	X	X[e]	X	X	X	X		X[f]
Randomization	6.4	Randomization to occur ≤ 3 days prior to dosing.		X																	
ECG (12-lead)	8.3.4	At screening and as clinically indicated.	X																		X[f]
Hematology[j]	8.3.6			X	X[e]	X	X	X	X	X	X[e]	X	X	X	X[e]	X	X	X	X		X[f]
Serum chemistry[j,k]	8.3.6			X	X[e]	X	X	X	X	X	X[e]	X	X	X	X[e]	X	X	X	X		X[f]
Coagulation factors[j]	8.3.6			X	X[e]						X[e]				X[e]		X	X	X		X[f]
Endocrine[j]	8.3.6	TSH, T3, and T4 measured only at screening, C2D1 (or ≤2d before C2D1), and on D1 of every even cycle thereafter (or ≤2d before the respective D1).		X	X[e]						X[e]				X[e]		X	X[l]	X[l]		X[f]
Urinalysis[j]	8.3.6			X	X[e]						X[e]				X[e]		X				X[f]
Pregnancy test	8.3.6			X[m]	X[e,n]						X[e,n]				X[e,n]		X	X	X		X[f]
HCV, HBV	8.3.6	HBV (HBsAg, HBV DNA and anti-HBc). HCV (anti-HCV and if positive, continue with HCV RNA)	X[m]																		X[f]
AEs[o]	8.4.1, 8.4.2	X*: AEs related to protocol-mandated procedures X#: No monitoring required after safety follow-up visit(s), but if investigator becomes aware of a trial treatment related SAE, it must be reported.	X*		X[e]	X	X	X	X	X	X[e]	X	X	X	X[e]	X	X	X	X	X[#]	X

Period			Screening		Treatment Period (42-Day Cycles)												Post-Treatment Period				UNS
Cycle/Visit	Section	Notes			Cycle 1-2						Cycle 3-4				Cycle 5 Onward[a]		EoT[b]	SFU1	SFU2	Survival FU[c]	
Day			≤28d prior to C1D1	≤7d prior to C1D1	D1	D8	D15	D22	D29	D36	D1	D8	D15	D22	D1	D22	-	60d after last dose	90d after last dose	Q12W after last dose	
Visit window					+3d or ±3d[d]	±2d	±2d	±2d	±2d	±2d	±3d	±2d	±2d	±2d	±3d	±3d		±5d	±7d	±14d	
Trial treatment administration	6.1, 6.3	Subjects who experience a delay in the administration of trial drug should return to the clinic at least Q3W (±3d). An unscheduled visit should be performed and reported in the eCRF. Unscheduled visit assessments should be performed at the investigator's discretion.			X						X				X						
Survival status	7.1.2.4	Starts from the date subject last received their trial treatment.																X	X	X[c]	X
Subsequent anti-cancer therapy	7.1.2.2																X	X	X	X	
CT/MRI/PET scan(s)	8.2.1.1, 8.2.1.2	CT and/or MRI performed ≤28d prior to C1D1 as SOC can be used for screening. Prior tumor scan images should be collected if feasible.	X (≤28d prior to C1D1)		On-trial imaging will be performed Q6W (±7d) for first 48w and then every 12 weeks (±7 days) until documented radiographic disease progression (as assessed by the investigator), start of subsequent anti-cancer therapy, withdrawal of consent, death, or loss to follow up, whichever occurs first. Imaging assessments should follow calendar days and should not be adjusted for delays in cycle starts.															
FACT-GP5	8.9.1	Subject questionnaires should be completed before any clinical assessments are conducted and before receiving any trial treatment.[p]			X			X			X			X	X	X					
FACT-M	8.9.2				X						X				X						
Tumor biopsy (fresh/archival); biomarkers	8.7.1		X		Refer to Table 2																
PK/ADA sampling	8.5, 8.8				Refer to Table 3																

Abbreviations: ADA=anti-drug antibody; AE=adverse event; CT= computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EoT=end of treatment visit; FU=follow up; HBV=hepatitis B virus; HCV=hepatitis C virus; ICF=informed consent form; IMP=investigational medicinal product; irAE=immune-related adverse event; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic(s); PRO=patient-reported outcome; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SFU=safety follow up visit; SOC=standard of care; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; UNS=unscheduled visit.

[a] Subsequent cycles until discontinuation criteria are met (see Section 7.1.1).

[b] If the subject shows disease progression or confirmed radiographic disease progression (as per RECIST v1.1) or is discontinued from treatment due to another reason, the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of trial drug.

[c] Survival status may be collected via telephone, email, visit, or other records (see Section 7.1.2.4).
[d] A visit window of ±3d is allowed for C2D1.
[e] All Day 1 assessments (including AE evaluation) and investigations must be performed and checked by the investigator prior to administration of trial treatment.
[f] To be collected at unscheduled visits only if relevant.
[g] History of COVID-19 and/or influenza infections, including dates of onset and resolution and registration on any related on-going AEs, within 6 months prior to C1D1 should be recorded in the eCRF if known/ applicable.
[h] Prior to enrollment, subjects should be up to date on recommended prophylactic vaccines including but not limited to seasonal vaccines (COVID-19, influenza, RSV) as well as age- and risk-based vaccines (herpes zoster, pneumococcal, Tdap) adhering to the ASCO guidelines (Kamboj et al., 2024). The type and timing of all vaccines received in the last 6 months need to be appropriately entered in the eCRF (Section 6.6.2).
[i] Covid 19 booster vaccine is strongly recommended during screening if none was given in the last 2 months, based on the ASCO guidelines (Kamboj et al., 2024). The COVID-19 booster needs to be administered ≥ 2 weeks before C1D1; mRNA-based COVID-19 vaccines are recommended.
[j] C1D1 labs are not required if laboratory assessments for screening and baseline meet eligibility thresholds and were performed within 3 days of first dose. Dosing day laboratory assessments must be obtained within 3 days, preferably on the day of IMP administration and reviewed by the investigator prior to IMP trial drug administration.
[k] Sampling for procalcitonin is advised as soon as a serious/Grade ≥ 3 irAE is suspected to rule out bacterial infection as cause of inflammation.
[l] 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.
[m] Samples must be collected at minimum 5 days prior to planned C1D1.
[n] A urine pregnancy test at C1D1 should be performed by the local laboratory. If the local urine pregnancy test is positive, a confirmatory serum pregnancy should be performed. A negative urine or serum test must be available prior to dosing on C1D1. For all other cycles on D1, a urine pregnancy test should be performed locally (serum confirmatory testing is not required).
[o] Sample for cytokines/soluble factors analyses to be taken as soon as a serious/Grade ≥ 3 irAE is suspected (see Table 2).
[p] Exception if subjects are hospitalized and clinical tests need to be done immediately, ePROs may then be conducted post those assessments.

Table 2: Schedule of Biomarker Assessments

Treatment Cycle	Screening	Cycle 1-2		Cycle 3	End of Treatment Visit	Unscheduled Visit
Day	**≤28d prior to C1D1**	**D1**	**D8**	**D1**		
Visit window		**+3d or ±3d[a]**	**±2d**	**±3d**		
Tumor tissue (fresh biopsy and/or archival tissue)	X[b]				X[c]	X[d]
Cytokines and soluble factors (serum)		X[e]	X	X[e]		X[f]
Immune phenotyping (PBMCs)		X[e]	X	X[e]	X	
ctDNA (plasma)		X[e]		X[e]	X	

Abbreviations: ctDNA=circulating tumor-derived DNA; D/d=day; DNA=deoxyribonucleic acid; FFPE= formalin fixed paraffin embedded; irAE=immune-related adverse event; PBMCs=peripheral blood mononuclear cells

[a] A visit window of ±3d is allowed for C2D1.

[b] All subjects must provide an FFPE tumor tissue sample that originates from the advanced and/or metastatic melanoma setting (ie, Stage IIIB, IIIC, IIID, or IV). Fresh tumor biopsy (defined as ≤ 3 months old) is preferred; archival tumor tissue is acceptable. If a fresh tumor sample is provided, it needs to be collected after progression on or discontinuation of last prior treatment and prior to C1D1. Please refer to Section 8.7.1 for additional information on the tumor tissue requirements.

[c] If clinically feasible, tumor biopsies should be performed at disease progression, preferably from a newly diagnosed lesion, if any.

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

[e] Collected prior to trial treatment infusion.

[f] As soon as a serious/Grade ≥ 3 irAE is suspected, a sample for cytokines/soluble factors analyses should be collected. Additional unscheduled sample collections for cytokines/soluble factors may be performed if deemed necessary by the investigator.

Table 3: Schedule of PK and ADA Sampling

Treatment Cycle/Visit	Cycles 1-2					Cycles 3-4			Cycle 5 Onward[a]		EOT	SFU1	SFU2	UNS
Day	D1		D8	D15	D22	D1		D8	D1					
Visit window	+3d or ±3d[b]		±2d	±2d	±2d	±3d		±2d	±3d			+5d	±7d	
Window (relative to acasunlimab dosing)	Pre[c]	EOI (+15 min)				Pre[c]	EOI (+15 min)		Pre[c]	EOI (+15 min)				
Acasunlimab PK	X	X	X	X	X	X	X	X	X[a]	X[a]	X	X	X	X[d]
Acasunlimab ADA	X					X			X[a]		X	X	X	
Soluble target	X		X			X			X[a]		X	X	X	

Abbreviations: ADA=anti-drug antibody; D/d=day(s); EOI=end of infusion; EOT=end of treatment; PK=pharmacokinetic(s); Pre=predose; SFU=safety follow-up; UNS=unscheduled.

[a] Cycle 5, Cycle 7, and every 2 cycles thereafter (Cycles 9, 11, 13, etc).

[b] A visit window of ±3d is allowed for C2D1.

[c] Predose sampling to be collected prior to beginning of any trial treatment infusion.

[d] Assessment optional at unscheduled visit.

2 INTRODUCTION

2.1 Background

2.1.1 Disease Background

Epidemiology data from Globocan 2022 reported there were approximately 330,000 cases of melanoma worldwide, amounting to just under 2% of all cancers, and approximately 60,000 deaths per year due to melanoma (0.6% of cancer-related mortality) (Bray et al., 2024). The annual incidence of cutaneous melanoma has increased over the past 50 years, with approximately 25 new cases per 100,000 population in Europe, 30-cases per 100,000 population in the USA, and around 50 new cases per 100,000 population in Australia and New Zealand. It is largely found in White Caucasian populations, where exposure to ultraviolet radiation is a predisposing factor for the development of this cancer. Certain subtypes of melanoma (eg, acral) have been identified in Black and Asian populations (Long et al., 2023).

Until approximately 2010, the mainstay of treatment for metastatic melanoma was cytotoxic chemotherapy, of which dacarbazine was the only therapy that was licensed for this indication in the 1970's (US only) (Serrone et al., 2000). With dacarbazine treatment, survival outcomes were poor (median OS ranged from 6-8 months) with response rates between 7-12% (Chapman et al., 2011). The introduction of novel immunotherapies and targeted therapies have improved outcomes for patients with metastatic cutaneous melanoma.

Immunotherapy

The emergence of approved CPIs has transformed the treatment paradigm for metastatic cutaneous melanoma, becoming the 1L SOC for patients, with recent data favoring their use prior to treatment with BRAF/MEK inhibitors in patients with BRAF-mutated disease (Ascierto et al., 2023).

When the first approved CPI ipilimumab (anti–CTLA-4 mAb) was combined with the CPI nivolumab (anti–PD-1 mAb) in the CheckMate-067 trial, a median PFS of 11.5 months was reported in treatment-naive subjects, with an ORR of 58%. Grade 3-4 treatment-related AEs were reported in 55% of subjects, which was higher than reported with the monotherapies in this trial and previous studies (Larkin et al., 2015). With a minimum follow up of 10 years, the median OS was 71.9 months with nivolumab plus ipilimumab, 36.9 months with nivolumab, and 19.9 months with ipilimumab, and no new safety signals were reported (Wolchok et al., 2025). Another novel combination therapy, nivolumab with relatlimab (anti-LAG3 mAb), demonstrated a PFS that was comparable to data with nivolumab + ipilimumab reported in CheckMate-067 (Tawbi et al., 2022). The combination demonstrated an ORR of 43% (95% CI: 38-48) (Opdualag USPI, 2024).

Pembrolizumab (anti–PD-1 mAb) demonstrated an ORR of approximately 30% in subjects who were refractory to ipilimumab in the Phase 3 Keynote-006 trial (see Section 2.1.3); median OS was approximately 40 months with 5-years of follow-up. Combination therapy with pembrolizumab, which is relevant for the GCT1046-07 trial, is further discussed in Section 2.1.3.

The safety profile of CPIs has been found to be manageable, with immune-related toxicities (eg, pneumonitis, colitis) requiring a level of experience to manage, including where intervention has been required with steroids and possibly other immunosuppressive drugs, and where life-threatening grades of these events have occurred in patients. Some toxicity has been potentially life-changing (eg, thyroiditis, hypophysitis).

Recently, lifileucel, a tumor-derived autologous T-cell immunotherapy, received accelerated approval in the US for the treatment of patients with unresectable locally advanced or metastatic melanoma previously treated with a PD-1 blocking antibody (and targeted therapy with a BRAF inhibitor ± MEK inhibitor if BRAF V600 mutation positive). An ORR of 31.5% (95% CI: 21.1, 43.4), with a median DOR that was NR (95% CI 4.1, NR), was reported in the Phase 2 single-arm C-144-01 trial (Chesney et al., 2022). Over 95% of subjects experienced a Grade 3 AE, and almost 88% experienced a Grade 4 AE. However, approximately 70% of subjects in the trial did not respond to treatment with lifileucel, treatment involves a multistep process including lymphodepletion and high-dose IL-2 infusions and requires specialized facilities and medical expertise, making this therapy less accessible. Therefore, there is still an unmet medical need and the need to continue developing new therapies.

Targeted Therapy

The use of BRAF and MEK inhibitors is well established as 1L treatment of BRAF V600 (mostly BRAF V600E) mutation-positive melanoma (around 50% of all melanoma patients).

Dabrafenib in combination with trametinib was the first approved BRAF/MEK inhibitor combination therapy, with the most recently approved combination being encorafenib and binimetinib. Both combinations showed similar response rates at just over 60%. Although there are no direct comparative data, the encorafenib + binimetinib combination provided more favorable PFS compared to the other licensed combination BRAF/MEK therapies, as reported in a network meta-analysis (HR=0.88; 95% CI 0.66, 1.18 versus dabrafenib/trametinib; HR=0.89; 95% CI 0.63, 1.25 versus vemurafenib/cobimetinib) (Corrie et al., 2022).

The safety profiles of these targeted therapies involved events that were largely associated with tyrosine kinase inhibition (eg, arthralgia, rash), whereas photosensitivity and pyrexia were associated with BRAF inhibition, and ocular toxicity (reversible retinal detachment) was found related to MEK inhibition.

Triplet Combination and Sequencing of Therapy

While the onset of action of selective BRAF inhibitors appears to be faster than with CPIs such as pembrolizumab, the effect is less durable and once progression occurs, patients can deteriorate quickly. Targeted therapy was shown to be particularly useful in treating patients with aggressive or bulky disease or symptomatic brain metastases. Evidence suggests that while patients do better within the first 12 months of targeted therapy, CPIs tend to confer more durable responses.

Clinical studies are being conducted to see how best to optimize the use of both immunotherapies and targeted therapies for patients with BRAF-mutated melanoma. The Phase 3 KEYNOTE-022 trial evaluating the triplet combination of dabrafenib/trametinib and pembrolizumab in treatment-naive subjects reported an ORR of 63.3%, a median PFS of

16.9 months, and 24-month OS rate of 63% (Ferrucci et al., 2020). The Phase 3 studies, IMspire150 (vemurafenib, cobimetinib, atezolizumab) and COMBI-i (dabrafenib, trametinib, spartalizumab), demonstrated clinical outcomes that broadly reflected those seen in the KEYNOTE-022 trial, although there were differences in the baseline prognostic indicators (Ascierto et al., 2023; Dummer et al., 2022).

Alternative treatment strategies attempted to find the optimal sequencing of CPIs and targeted therapies for BRAF V600 mutated metastatic melanoma, eg, the SECOMBIT Phase 2 trial (Ascierto et al., 2023). The authors concluded that subjects received clinical benefit from 1L immunotherapy with CPIs, followed by targeted therapy. The DREAMseq Phase 3 trial further supported this conclusion (Atkins et al., 2023). This practice is reflected in current treatment guidelines (Garbe et al., 2022; NCCN, 2024). Per NCCN guidelines, patients with BRAF-mutated melanoma who have received and progressed on prior lines of therapy including CPI therapy and targeted BRAF/MEK inhibitor therapy, may receive rechallenge with CPI monotherapy or as combination therapy

For patients with BRAF wild-type disease who have progressed on prior lines of SOC therapies, the NCCN recommends the same treatment options as described for patients with BRAF-mutated melanoma (apart from rechallenge with BRAF/MEK inhibitor therapy). European consensus guidelines are broadly aligned with NCCN guidelines (Garbe et al., 2022; NCCN, 2024).

Beyond 2L therapy, other recommended treatment options include cytotoxic chemotherapy, high-dose IL-2, or for low-burden disease including lesions that are easily accessible for injection, treatment with ipilimumab and talimogene laherparepvec (T-VEC), a herpes simplex virus type 1–derived oncolytic immunotherapy. Treatment within clinical studies is also recommended. Patients who have exhausted all current options may be treated with either chemotherapy or best supportive care, as recommended by both NCCN and European Consensus guidelines.

In view of the limited systemic therapeutic options for patients with advanced unresectable melanoma, regardless of BRAF mutation status, who have exhausted all potential SOC therapies, there is a clear unmet need, underscoring the requirement to explore novel treatment modalities to improve responses rates and survival in this patient population.

The purpose of this trial is to investigate the efficacy and safety of acasunlimab as monotherapy and in combination with pembrolizumab in adult subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma (BRAF wild type or mutant) that progressed on or after prior CPI-containing therapy.

2.1.2 Acasunlimab Background

Acasunlimab (GEN1046; DuoBody®-PD-L1×4-1BB) is a bispecific antibody targeting PD-L1 and 4-1BB. Acasunlimab has a regular IgG1 structure and biochemical characteristics typical of a human IgG1 antibody.

The MoA of acasunlimab is distinct from that of conventional PD-L1 blocking and 4-1BB targeting IgG mAbs.

Acasunlimab induces activation of T cells through conditional 4-1BB stimulation that is strictly dependent on simultaneous binding to PD-L1, while conventional 4-1BB-targeting

antibodies are typically dependent on agonist activity through FcγR-mediated antibody crosslinking (Chin et al., 2018). The Fc domain of acasunlimab was engineered to silence interactions with FcγR and the complement component 1q (C1q), thereby abrogating 4-1BB agonist activity through FcγR-mediated crosslinking of membrane-bound acasunlimab, as well as cytotoxic activity mediated by FcγR- or complement-mediated effector functions. By this molecular engineering, 4-1BB agonist activity by acasunlimab is conditional, ie, it is dependent on simultaneous binding of acasunlimab to both 4-1BB and PD-L1, and binding of acasunlimab to 4-1BB in the absence of PD-L1 expressing cells does not induce agonist activity (Muik et al., 2022b).

In addition to the conditional 4-1BB stimulation, the PD-L1-specific arm of acasunlimab also functions as a classical CPI by blocking the PD-1/PD-L1 axis, independent of 4-1BB binding (Muik et al., 2022b).

2.1.2.1 Nonclinical Summary

Acasunlimab was shown to enhance CD4+ and CD8+ T-cell proliferation, proinflammatory cytokine secretion (primarily IFNγ) and T-cell–mediated cytotoxicity in vitro and patient-derived TIL expansion ex vivo (Muik et al., 2022b). Proof-of-concept that dual targeting of PD-L1 and 4-1BB using an Fc-silenced bispecific PD-L1×4-1BB antibody (mouse reactive mbsIgG2aPD-L1×4-1BB) induces antitumor activity in vivo was demonstrated in mice bearing subcutaneous CT26 or MC38 tumors (Muik et al., 2022a). In transgenic C57BL/6 mice expressing the extracellular domains of human PD-L1 and human 4-1BB, acasunlimab induced a potent antitumor immune response, leading to complete regression of subcutaneous MC38 tumors expressing human PD-L1, and conferred protection against secondary tumor challenge in vivo (Muik et al., 2022b).

In GLP toxicity studies in cynomolgus monkeys for up to CCI , IV infusion of acasunlimab did not induce any adverse acasunlimab-related toxicological, pathologic, or safety pharmacology-related findings. The NOAEL and the highest non-severely toxic dose for acasunlimab are considered CCI .

For additional details regarding nonclinical studies, refer to the acasunlimab IB. A summary of nonclinical data supporting the combination of acasunlimab with an anti-PD-1 CPI is provided in Section 2.2.2.

2.1.2.2 Clinical Summary

Other studies investigating acasunlimab as monotherapy or as part of combination therapy in subjects with various advanced solid tumors include:

- GCT1046-01 is an FIH, open-label, dose-escalation and expansion trial in adult subjects with malignant solid tumors, including NSCLC, urothelial carcinoma, endometrial cancer, TNBC, squamous cell carcinoma of the head and neck, and cervical cancer.
- GCT1046-02 is a Phase 1 acasunlimab dose-escalation trial with a pembrolizumab combination cohort conducted in Japan; the safety and PK of acasunlimab as monotherapy or in combination with pembrolizumab was assessed in Japanese subjects with advanced and/or metastatic tumors.
- GCT1046-04 is a Phase 2, randomized, open-label trial of acasunlimab as monotherapy and in combination with pembrolizumab in subjects with

relapsed/refractory metastatic NSCLC after treatment with SOC therapy containing an immune CPI.

- GCT1046-06 is a Phase 3, randomized, open-label trial of acasunlimab in combination with pembrolizumab vs docetaxel in subjects with PD-L1 positive, metastatic NSCLC after treatment with a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy.

Acasunlimab as monotherapy and in combination with pembrolizumab showed a manageable safety profile and promising clinical activity in subjects with select advanced solid tumors.

Refer to clinical data supporting the combination of acasunlimab and pembrolizumab in Section 2.2.2.

For additional details regarding PK, safety, and efficacy, refer to the acasunlimab IB.

2.1.3 Pembrolizumab Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity and affinity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2 and resulting in potent PD-1 receptor blocking activity. Pembrolizumab has an acceptable clinical safety profile as an IV immunotherapy and is indicated for the treatment of patients across a number of indications, including unresectable or metastatic melanoma (Herbst et al., 2016; Paz-Ares et al., 2018; Reck et al., 2016; Rodríguez-Abreu et al., 2021).

The Phase 1b KEYNOTE-001 trial evaluated subjects with melanoma who were treatment-naive, ipilimumab- naive or who had received prior therapy with it. Doses of 2 mg/kg Q3W were compared to 10 mg/kg doses given Q2W or Q3W. Median OS ranged from 23-25 months, with the longest outcomes provided by the 10 mg/kg Q2W dose. OS rates were around 50% across all doses at 2 years of follow up, and around 40% at 3 years. The median OS and 24- and 36-month OS rates were 20 months and 46% and 41%, respectively, for ipilimumab-treated subjects, approximately 29 months and 54% and 41%, respectively, for ipilimumab-naive subjects, and 32 months and 60% and 45%, respectively, for treatment-naive subjects (Robert et al., 2016). Median PFS was 8.3 months for all subjects and 16.9 months for treatment-naive subjects. At the 5-year follow up, the estimated OS was 34% in all subjects and 41% in treatment-naive subjects. Grade 3/4 treatment-related AEs were reported in 17% of subjects (Hamid et al., 2019).

The Phase 3 KEYNOTE-006 trial (evaluating subjects with unresectable Stage 3 or Stage 4 melanoma who had progressed on 1 prior line of systemic therapy [excluding CTLA-4 inhibitors and anti-PD-1/PD-L1 therapies]), evaluated pembrolizumab monotherapy 10 mg/kg Q2W and Q3W versus ipilimumab 3mg/kg Q3W (up to 4 doses). Results showed superior survival outcomes with pembrolizumab compared to ipilimumab. Both regimens of pembrolizumab showed 6-month PFS rates of almost 50%, which were approximately twice that reported with ipilimumab; 12-month OS rates were also superior with pembrolizumab (74.1% [Q2W] and 68.4% [Q3W]) versus with ipilimumab (58.2%) (Robert et al., 2015). ORRs with pembrolizumab were approximately 30%, which was about 3 times that reported with ipilimumab. Survival outcomes were maintained at 7 years (Robert et al., 2023).

The results favored treatment with pembrolizumab, regardless of BRAF mutation status, prior treatment with BRAF/MEK inhibitor therapies, and other prognostic indicators. However, the data demonstrated that while monotherapy provides reasonably durable responses, around

70% of subjects do not benefit from this monotherapy, demonstrating the unmet need and an opportunity for investigation of novel combination therapies.

The administration of pembrolizumab 400mg Q6W was approved by the FDA, based upon comparative PK modeling and exposure-response analyses. PK and efficacy data were obtained from Cohort B of the KEYNOTE-555 single-arm trial of subjects (n = 101) with metastatic melanoma who had not received prior anti-PD-1/PD-L1 or CTLA-4 therapy. ORRs were approximately 50% (Cohen et al., 2024; Jacobs et al., 2021; Lala et al., 2020). In a small Phase 2 trial, pembrolizumab (200 mg Q3W) was combined with ipilimumab (1 mg/kg Q3W) in subjects with metastatic melanoma who had progressed on initial anti-PD-1/L1 therapy (Olson et al., 2021). ORR was 29%, while median PFS and OS were 5 months and 24.7 months, respectively. Grade 3/4 treatment-related AEs were reported in 27% of subjects.

For more details on specific indications, refer to the local pembrolizumab prescribing information.

For additional information on the rationale for the combination with acasunlimab, refer to Section 2.2.2.

2.2 Trial Rationale

Although PD-1/PD-L1 inhibitors as monotherapy or in combination with other systemic therapies have been approved as 1L therapies for melanoma, there remains a need to improve long-term outcomes, and resistance to these therapies remains a major challenge. Based on results of KEYNOTE-006 (pembrolizumab), CHECKMATE-067 (nivolumab and nivolumab + ipilimumab), and RELATIVITY-047 (nivolumab + relatlimab) studies, 33%-50% of subjects with previously untreated unresectable or metastatic melanoma respond to treatment with anti-PD-1 monotherapy or in combination with another immune CPI (Keytruda USPI, 2024; Opdivo USPI, 2024; Opdualag USPI, 2024; Yervoy USPI, 2023). However, ≥ 50% of subjects in these studies did not respond to treatment and PFS results indicated that ≥ 50% of subjects experienced progressive disease within 1 year.

For patients who have received and progressed on prior lines of therapy, including CPI therapy (and targeted BRAF/MEK inhibitor therapy for BRAF-mutated patients with advanced melanoma), they may go on to receive rechallenge with CPIs (either as monotherapy or combination therapy). Beyond these options, alternative therapeutic options are recommended by NCCN and European Consensus guidelines, although data is limited and not all patients derive compelling responses. The provision of an additional systemic immunotherapy option would be desirable before resorting to management of advanced melanoma with either chemotherapy or best supportive care.

Acasunlimab could provide favorable responses in a treatment setting following prior CPI-containing regimen(s) (for additional details see Section 2.2.1). This is based upon the responses observed with acasunlimab monotherapy in subjects with metastatic NSCLC previously treated with a PD-1/PD-L1 inhibitor in the GCT1046-01 trial. The addition of pembrolizumab may further potentiate this efficacy (for additional details see Section 2.2.2). The combination of pembrolizumab with a PD-L1/4-1BB bispecific mAb has not been evaluated previously in subjects with advanced melanoma and will be assessed in this trial.

While several small Phase 2 studies have already been conducted in subjects with unresectable locally advanced or relapsed/refractory metastatic melanoma who have progressed on prior CPI therapy (see Section 2.1.1), there remains the need for novel therapies to improve clinical outcomes in this setting. Bispecific antibodies that combine blockade of immune CPIs with conditional T-cell co-stimulation (eg, via 4-1BB) hold great promise. By fully harnessing the adaptive immune response, these agents aim to reinvigorate antitumor immunity and elicit durable responses, potentially overcoming resistance to classical CPIs.

The objectives of this trial are to investigate the efficacy and safety of acasunlimab as monotherapy and in combination with pembrolizumab in adult subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma (BRAF wild type or mutant) that progressed on or after prior treatment with CPI-containing therapy.

2.2.1 Rationale for Acasunlimab Monotherapy

Given that the clinical activity of anti-PD-(L)1 agents in melanoma may be constrained by T-cell exhaustion mechanisms, acasunlimab's ability to provide conditional 4-1BB stimulation—strictly dependent on PD-L1 binding within the tumor and/or lymphoid tissues—offers a potential strategy to reinvigorate anti-tumor immunity and deliver clinical benefit in the post-CPI setting. Supporting this, preclinical studies demonstrate that acasunlimab can reverse T-cell dysfunction in vitro (Blum et al., 2022). Single-agent acasunlimab has shown a manageable safety profile and early clinical activity in heavily pretreated subjects with advanced solid tumors, including those who had progressed on prior CPI-containing therapy.

In the FIH clinical trial GCT1046-01, confirmed objective responses were observed following treatment with acasunlimab 100 mg Q3W in a PD-L1 unselected, heavily pretreated population of subjects with metastatic NSCLC who had received prior treatment with a PD-1/PD-L1 inhibitor. The safety profile of acasunlimab was acceptable across several expansion cohorts. The most common related TEAEs (grouped events) were hepatic events that mainly manifested as asymptomatic liver transaminase elevations. Refer to the acasunlimab IB for additional details.

Although acasunlimab has not yet been tested for the treatment of melanoma, another bispecific antibody targeting PD-L1 and 4-1BB, FS222, recently demonstrated early promising single-agent antitumor activity (confirmed ORR of 46.7%; 7/15) in subjects with cutaneous melanoma previously treated with an anti-PD-1 therapy (Garralda et al., 2024). These results support the potential of PD-L1 and conditional 4-1BB bispecific targeting to provide clinical benefit in melanoma following progression on prior anti-PD-(L)1 agents and provide further rationale for evaluating acasunlimab monotherapy in this setting.

See Section 4.3.1.1 for the acasunlimab dose and schedule rationale.

2.2.2 Rationale for Acasunlimab in Combination with Pembrolizumab

Since 4-1BB is often co-expressed with PD-1 on $CD8^+$ T cells, blockade of the PD-1/PD-1 ligand (both PD-L1 and PD-L2) axis and simultaneous co-stimulation through 4-1BB may synergize to enhance T-cell effector functions and improve the duration of the response (Kim et al., 2020). This hypothesis is supported by clinical PK and pharmacodynamic findings

(Bajaj et al., 2021) as well as preclinical in vitro studies with human immune cells and in vivo animal studies (Capello et al., 2023; Capello et al., 2024) showing that the combination of acasunlimab or a mouse reactive PD-L1×4-1BB bispecific antibody and a PD-1 inhibitor induced synergistic immunomodulatory and antitumor effects compared to each agent alone. In a Phase 2 trial (GCT1046-04), the combination of acasunlimab 100 mg and pembrolizumab Q6W was shown to improve durability of response and OS versus acasunlimab monotherapy and acasunlimab plus pembrolizumab Q3W, as well as have a manageable safety profile as 2L therapy for subjects with PD-L1+ metastatic NSCLC (Aerts et al., 2024). In the combination arms, the most common treatment-related AEs (all grades) were asthenic condition and hepatic events and the most common treatment-related AEs of Grade ≥ 3 were hepatic events. Most liver-related events were asymptomatic immune-mediated transaminase elevations that were manageable with steroids and/or treatment delay. Early peripheral pharmacodynamics were consistent with acasunlimab-mediated immune activation in all arms, with a more pronounced increase in CD8+ T-cell proliferation with the combination therapy.

See Section 4.3.1.1 for the acasunlimab dose and schedule rationale. Refer to the acasunlimab IB for additional nonclinical and clinical information supporting the combination.

2.3 Benefit-Risk Assessment

2.3.1 Potential Benefit

New treatment options are needed to further improve long-term outcomes for patients with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma who have progressed on or after CPI therapy. In the GCT1046-01 and GCT1046-04 studies, acasunlimab monotherapy has demonstrated early antitumor activity in heavily pretreated subjects with selected advanced solid tumors, including those previously treated with CPI-containing therapy. PK and pharmacodynamic clinical findings, as well as a breadth of preclinical studies, suggest that combining acasunlimab with a PD-1 inhibitor may further potentiate antitumor activity and extend durability of clinical responses (see Section 2.2.2). Acasunlimab in combination with pembrolizumab has a manageable safety profile and demonstrated promising antitumor activity in subjects with PD-L1–positive metastatic NSCLC with progression after ≥ 1 prior anti PD-(L)1 containing treatment.

2.3.2 Potential Risks

2.3.2.1 Acasunlimab Monotherapy

Acasunlimab has not been evaluated for the treatment of subjects with melanoma. However, based on data from ongoing Phase 1/2 clinical studies, acasunlimab demonstrates a manageable safety profile in subjects with other select solid tumors. The most common treatment-related AEs with acasunlimab monotherapy are hepatic events (ALT and AST increases). Hepatic events are important identified risks and require careful monitoring and early management. Additionally, HLH represents an important potential risk, emphasizing the need for vigilance as it can initially present with minimal symptoms. Other identified risks include neutropenia and febrile neutropenia, while potential immune-mediated risks may involve enterocolitis/colitis, decreased platelet count, and hyperglycemia.

A mitigation plan for close monitoring, diagnostic workup, and management of irAEs including immune-mediated hepatitis, neutropenia, thrombocytopenia, pneumonitis, colitis, hyperinflammatory syndromes as well as IRRs is outlined in Sections 6.7.1.2, 6.7.1.3, and Section 6.7.1.4, and Table 8.

All subjects enrolled in this trial will be monitored closely by qualified healthcare professionals who will provide care and evaluate the subject's response to the trial medication in terms of its safety and efficacy.

Furthermore, the sponsor Safety Committee will periodically monitor subject safety throughout the trial as described in Section 10.1.8.

For a comprehensive overview of the safety profile, including hepatic risks and HLH associated with acasunlimab, refer to the acasunlimab IB.

2.3.2.2 Acasunlimab and Pembrolizumab Combination Therapy

The combination of acasunlimab with pembrolizumab has not been studied in melanoma but has demonstrated a manageable safety profile in subjects with NSCLC in the post-CPI setting, with overlapping toxicities largely consisting of irAEs. Key potential irAEs include immune-mediated hepatitis, neutropenia, thrombocytopenia, pneumonitis, colitis, hyperinflammatory syndromes, and IRRs. A robust monitoring and mitigation strategy is essential and has been outlined in detail in Section 6.7.1.2, Section 6.7.1.3, Section 6.7.1.4, and Table 8. This plan includes guidance on diagnostic evaluations and proactive management for irAEs.

Qualified healthcare professionals will closely monitor all trial subjects to ensure timely identification and management of AEs, with ongoing assessments to evaluate both safety and efficacy. For a comprehensive overview of the safety profile, including hepatic risks and HLH associated with acasunlimab, refer to the acasunlimab IB. Refer to Section 6.7 for details on toxicity management.

2.3.2.3 Non-Genmab IMPs and AMPs

Please refer to the current prescribing information for pembrolizumab (IMP), and dexamethasone, methylprednisolone, prednisone, or equivalent (AMP) for information about associated risks.

2.3.3 Conclusion

Acasunlimab, as both a monotherapy and in combination with pembrolizumab, has demonstrated manageable safety and tolerability across various solid tumor types in previous and ongoing clinical studies, though it has not yet been studied in melanoma. Overall, acasunlimab, either as monotherapy or in combination, may offer clinical benefit for subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma who have progressed on or after previous CPI-containing therapies.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
Evaluate the antitumor activity of acasunlimab as monotherapy and in combination with pembrolizumab.	ORR assessed by the investigator per RECIST v1.1
Secondary	
Evaluate the time to onset and durability of the antitumor response of acasunlimab as monotherapy and in combination with pembrolizumab.	• TTR assessed by the investigator per RECIST v1.1 • DOR assessed by the investigator per RECIST v1.1
Evaluate PFS and OS in subjects treated with acasunlimab as monotherapy and in combination with pembrolizumab.	• PFS assessed by the investigator per RECIST v1.1 • OS
Assess the safety and tolerability of acasunlimab as monotherapy and in combination with pembrolizumab.	• Occurrence and severity of AEs • Time to treatment discontinuation due to AE
Exploratory	
• Explore biomarkers in tumor specimens and peripheral blood as potential predictors of acasunlimab efficacy outcomes as monotherapy and in combination with pembrolizumab. • Assess pharmacodynamic markers in peripheral blood to evaluate immune system activation and modulation by acasunlimab as monotherapy and in combination with pembrolizumab. • Explore changes in ctDNA variant levels as a surrogate marker for clinical activity	Biomarker levels during the trial and the change from baseline
Characterize the PK and immunogenicity of acasunlimab as monotherapy and in combination with pembrolizumab.	Acasunlimab PK concentrations and ADAs
Assess the change in overall quality of life and melanoma-related symptoms in subjects treated with acasunlimab as monotherapy and in combination with pembrolizumab.	Change from baseline in FACT-M total, FACT-M Trial Outcomes Index, and FACT-M melanoma subscale
Assess the overall side-effect burden in subjects treated with acasunlimab as monotherapy and in combination with pembrolizumab.	Proportion of subjects with high side-effect burden (response ≥ 3) (FACT-GP5)

Abbreviations: ADA=anti-drug antibody; AE=adverse event; ctDNA= circulating tumor deoxyribonucleic acid; DOR=duration of response; FACT-GP5= Functional Assessment of Cancer Therapy-General item GP5; FACT-M= Functional Assessment of Cancer Therapy–Melanoma; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors; TTR=time to response

Primary Estimand for ORR

The primary clinical question of interest is: What is the effect of acasunlimab as monotherapy and in combination with pembrolizumab in increasing the ORR per RECIST v1.1 (investigator assessed) in subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma regardless of trial intervention compliance, and while no new anticancer therapy is initiated prior to disease progression?

This question is addressed by the "while no new anticancer therapy" estimand and is described by the following attributes:

- Treatment condition: randomized trial intervention until documented disease progression or unacceptable toxicity. Trial intervention discontinuation prior to documented progression or death will be ignored.
- Population: subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma who have progressed on or after prior CPI-containing therapy (as described in Section 5)
- Endpoint: confirmed ORR per RECIST v1.1 as reported by the investigator
- Remaining intercurrent events handling:
  - Initiation of new anticancer therapy prior to disease progression or death: while no new anticancer therapy is initiated
  - Radiographic progression: while no documented progression is observed
- Population-level summary measure: odds ratio of ORR for acasunlimab monotherapy vs in combination with pembrolizumab
- Rationale for estimand: the interest lies in the treatment effect without the confounding effect of other anticancer therapy.

4 TRIAL DESIGN

4.1 Description of Trial Design

This is a Phase 2, randomized, open-label, multicenter trial evaluating the efficacy and safety of acasunlimab as monotherapy and in combination with pembrolizumab in adult subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma who progressed on or after prior CPI-containing therapy. A schema of the trial design is provided in Section 1.2.

After signing the ICF, subjects will enter a screening period of up to a maximum of 28 days prior to Cycle 1 Day 1 and eligible subjects (Section 5) will be randomized.

An overview of the treatment arms and target population is presented in Table 5. Refer to Section 6.1 for detailed treatment information.

Table 5: Overview of Treatment Arms

Arm	Target Population/Indication Setting	Trial Treatment
Arm A	Subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma that progressed on/after prior CPI(s)	Acasunlimab 100 mg Q6W + Pembrolizumab 400 mg Q6W
Arm B		Acasunlimab 100 mg Q6W

Approximately 90 subjects are planned to be treated in this trial (see Section 9.5 for sample size determination), ie, approximately 45 subjects treated in each arm. Subjects will be randomized in a 1:1 ratio to 1 of 2 arms and stratified based on:

- BRAF V600 mutational status: wild type vs mutant
- LDH levels: ≤ ULN vs > ULN

Refer to Section 6.4 for further details regarding randomization and stratification.

An interim analysis for futility is planned after approximately 20 subjects are evaluable for ORR in each arm (Section 9.4.1).

Subjects who discontinue from the trial will not be replaced.

Treatment will continue until 1 of the discontinuation criteria in Section 7 are met. If a subject discontinues treatment prior to disease progression, assessments will continue as described in the Schedule of Activities (Section 1.3). Crossover is not allowed within this trial. However, treatment beyond progression with acasunlimab in combination with pembrolizumab may be allowed on an individual basis following discussion with the sponsor (Section 6.9). Refer to Sections 7.1.2.1-7.1.2.4 for details regarding post-treatment follow-up visits.

A Sponsor Safety Committee will be established for this trial. Refer to Section 10.1.8 for details on committee structure.

4.1.1 Patient Input into Design

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

4.2 Trial Design Rationale

GCT1046-07 will evaluate acasunlimab monotherapy and acasunlimab in combination with pembrolizumab in subjects with relapsed/refractory, unresectable locally advanced or metastatic cutaneous melanoma who have progressed on/after prior treatment with a CPI. The rationale for evaluating acasunlimab monotherapy and acasunlimab in combination with pembrolizumab is provided in Section 2.2.1 and Section 2.2.2, respectively. Randomization and stratification will be used to minimize any bias in enrollment to either arm. BRAF mutational status and LDH are recognized as important prognostic factors in this indication and are used as stratification factors.

The planned duration of the trial will allow sufficient data to be collected to evaluate the primary (ORR) and secondary endpoints of the trial.

The evaluation of ORR as a primary endpoint is a widely accepted surrogate endpoint in relapsed/refractory melanoma, is objectively measured, and provides outcomes in a timely manner, allowing for informed and timely decisions on whether to continue treating this population of subjects with melanoma with acasunlimab.

The futility analysis planned after 20 subjects per arm are evaluable for ORR (Section 9.4.1) will allow for a faster and more efficient assessment of the benefit and safety of acasunlimab as monotherapy and in combination with pembrolizumab, potentially minimizing the number of subjects with melanoma exposed to trial drug if not beneficial or safe.

4.2.1 Other Trial Design Considerations

The trial population broadly reflects the patients who may progress on or after treatment with 1L+ CPI-containing therapy (eg, monotherapy or combination therapy with nivolumab + ipilimumab or nivolumab + relatlimab). The inclusion criteria allow for enrollment of subjects with or without BRAF V600 mutations and with or without prior BRAF/MEK inhibitor treatment. Subjects with a BRAF mutation should have received prior BRAF-directed therapy (with or without a MEK inhibitor) prior to enrollment in the trial, unless deemed not clinically indicated by the Investigator due to concurrent medical condition or prior toxicity.

4.3 Trial Treatment Dose and Schedule Rationale

4.3.1 IMP Dose and Schedule Rationale

4.3.1.1 Acasunlimab

In this trial, the dose of acasunlimab is 100 mg Q6W administered as an IV infusion over 30 minutes, either in combination with pembrolizumab (Arm A) or as monotherapy (Arm B).

In the Phase 2 trial, GCT1046-04, 2 dose schedules of acasunlimab (100 mg Q3W and 100 mg Q6W) were evaluated in combination with pembrolizumab in subjects with metastatic NSCLC after treatment with CPI-containing therapy. Acasunlimab 100 mg Q6W when given in combination with pembrolizumab resulted in more durable responses compared to acasunlimab 100 mg Q3W in combination with pembrolizumab, and the responses were deeper and more durable compared to acasunlimab monotherapy (refer to the acasunlimab IB for details). Further, exposures evaluated with acasunlimab Q6W treatment

were associated with lower risk of Grade ≥ 3 liver-related events compared to acasunlimab 100 mg Q3W when given in combination with pembrolizumab (Bajaj et al., 2024). Also, faster resolution of Grade ≥ 3 liver-related AEs was observed with Q6W dosing in the GCT1046-04 trial.

Additionally, less frequent acasunlimab dosing (Q6W) in combination with pembrolizumab led to intermittent modulation of soluble 4-1BB, a marker for target engagement, compared to sustained soluble 4-1BB induction with the Q3W regimen. This was accompanied by lower induction of CD8+ T-cell subsets expressing TIM3, a co-inhibitory receptor implicated in T-cell dysfunction, in the Q6W combination arm compared to Q3W (Bajaj et al., 2024). These findings indicate that intermittent 4-1BB activation with Q6W dosing may prevent T-cell dysfunction due to chronic stimulation by allowing a resting period for the T cells and resetting of the T-cell response (Weber et al., 2021), thereby improving the magnitude and quality of the antitumor immune responses. This supports the potential for increased durability of clinical responses with less frequent Q6W acasunlimab dosing, either as monotherapy or in combination with pembrolizumab.

4.3.1.2 Pembrolizumab

In Arm A, the dose of pembrolizumab for this trial is 400 mg Q6W administered as an IV infusion over 30 minutes (Table 6) per the approved label.

4.3.2 AMP Dose and Schedule Rationale

4.3.2.1 Dexamethasone or Methylprednisolone or Prednisone (or Equivalent)

May be administrated as reactive premedication to prevent irAEs (if episodes occurred in previous cycles of trial drug) or to manage immune-mediated hepatitis (Table 7).

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

4.4.1 Primary Completion Date

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

Primary completion is when all data has been collected to assess the primary endpoint for the primary analysis of ORR, ie, approximately 12 months after the last subject's first dose.

4.4.2 Estimated Trial Duration for an Individual Subject

The estimated trial duration for an individual subject is approximately 15 months, consisting of a 28-day screening period, an estimated 4-month treatment period (the duration of treatment is expected to vary for each subject), and an estimated 10-month post-treatment 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 trial contact (ie, final survival follow-up collection) shown in the Schedule of Activities (Section 1.3).

4.4.3 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.

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

5 TRIAL POPULATION

The appropriate written informed consent must be obtained before any trial-specific activities/procedures are performed. After signing the ICF, subjects will be assigned a unique subject identifier before undergoing any screening procedures. Subjects who meet all of the eligibility criteria may be enrolled (see Section 5.3).

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

NOTE: Investigators should ensure enrollment criteria are met and the eligibility review is completed. Investigators are invited to reach out to the sponsor's medical monitor for assistance or consultation, if needed. If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of trial treatment is given, the investigator must ensure subject fulfills all eligibility criteria prior to the first dose.

5.1 Inclusion Criteria

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

1. Must sign an ICF indicating that the purpose of the trial and the procedures required for the trial are understood and indicating that the subject is willing to participate in the trial. Where required by local or country specific regulations, each subject must sign a separate ICF indicating agreement to provide samples for genomic biomarker analysis (DNA and RNA).
2. Be ≥ 18 (or the legal age of consent in the jurisdiction in which the trial is taking place) years of age.
3. Subject has histologically or cytologically confirmed diagnosis of relapsed/refractory, locally advanced unresectable (Stage IIIB, IIIC, or IIID) or metastatic (Stage IV) cutaneous melanoma, per AJCC (8th edition) staging.
4. Subject must have radiographic progression based on RECIST v1.1 on or following ≥ 1 prior systemic therapy according to local and international guidelines, including a PD-1 blocking antibody treatment or combination treatment containing a PD-1 blocking antibody for relapsed/refractory, locally advanced unresectable (Stage IIIB, IIIC, or IIID) or metastatic (Stage IV) cutaneous melanoma.
    a. Subject must have received a minimum of 2 cycles of an approved PD-1 blocking antibody monotherapy or combination therapy, and a BOR based on RECIST v1.1 of CR, PR, or SD must be known and documented.
    b. Neoadjuvant and/or adjuvant systemic therapy count as the first line of prior systemic therapy if there is documented disease progression ≤ 6 months after completion of therapy.
    c. A confirmatory scan is required ≥ 4 weeks after initial evidence of progressive disease following treatment with CPI therapy, provided that the subject is clinically stable prior to Cycle 1 Day 1 in this trial (note: this second confirmatory scan can be performed during the screening period).

5. Subjects are eligible regardless of BRAF V600 mutational status (wild type or mutant). BRAF V600 mutational status must be determined by local assessment and documented prior to enrollment.
6. Subjects who do not have a known BRAF mutational status per local assessment must be willing to provide tissue for local BRAF testing and provide results within the screening period.
7. Subjects with a BRAF V600 mutation should have received prior BRAF-directed therapy (with or without a MEK inhibitor) prior to enrollment in the trial, unless deemed not clinically indicated by the Investigator due to concurrent medical condition or prior toxicity.
8. Must provide an FFPE tumor tissue sample that originates from the advanced and/or metastatic melanoma setting (ie, stage IIIB, IIIC, IIID, or IV). Fresh tumor biopsy (defined as ≤ 3 months old) is preferred; archival tumor tissue is acceptable. If a fresh tumor sample is provided, it needs to be collected after progression on or discontinuation of last prior treatment. Documentation of the tumor sample shipment (ie, airway bill number) must be submitted to the Sponsor. Please refer to Section 8.7.1 for additional information on the tumor tissue requirements.
9. At least 1 measurable target lesion, as defined by RECIST v1.1. Refer to Section 8.2.1.1 for additional information and Section 10.6 for response assessment criteria.
10. Subject has an ECOG PS of 0 or 1 within 7 days prior to Cycle 1 Day 1.
11. Subject has a life expectancy of ≥ 3 months.
12. Has acceptable laboratory test results within 7 days of Cycle 1 Day 1, as follows:

Parameter		**Result**
a.	CrCl	Glomerular filtration rate ≥45 mL/min/1.73 m2 according to the abbreviated Modification of Diet in Renal Disease equation.
b.	Serum ALT	≤ 1.5×ULN
c.	Serum AST	≤ 1.5×ULN
d.	Alkaline phosphatase	≤ 2.5×ULN NOTE: Only applicable if ALT/AST results are reported above the normal range.
e.	Total bilirubin	≤ ULN NOTE: A subject with Gilbert's syndrome may be included if total bilirubin is ≤ 3×ULN and direct bilirubin is ≤ 1.5×ULN
f.	Albumin	≥ 30 g/L
g.	Hemoglobin	≥ 9 g/dL (≥ 90 g/L or ≥ 5.6 mmol/L) NOTE: Criteria must be met without packed red blood cell transfusion within the 4 weeks prior to Cycle 1 Day 1. Subjects can be on stable dose of erythropoietin (≥ approximately 3 months).
h.	Absolute neutrophil count	≥ 1.5×10^9/L (>1500/μL) NOTE: Must be met without administration of growth factors within 4 weeks prior to Cycle 1 Day 1
i.	Platelet count	≥ 100×10^9/L (≥ 100,000/μL)

Parameter		Result
j.	Coagulation status	INR ≤ 1.5×ULN aPTT ≤ 1.5×ULN NOTE: Subjects receiving anticoagulant therapies should have the PT and aPTT within the therapeutic range of intended use of anticoagulants.
k.	LDH	< 2×ULN

13. A female subject with reproductive potential must agree to use adequate contraception during trial treatment, and for 4 months after receiving the last dose of trial treatment (acasunlimab and/or pembrolizumab). Reproductive potential and adequate contraception (ie, highly effective methods of contraception) are defined in Section 10.3.

    NOTE: If reproductive potential changes after start of the trial (eg, female with reproductive potential becomes sexually active) a female subject must begin adequate contraception (ie, highly effective methods of contraception), as described in Section 10.3.

14. A female subject with reproductive potential must have a negative serum beta-hCG at screening.
15. A female subject must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial treatment and for 4 months after receiving the last dose of trial treatment.
16. Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

5.2 Exclusion Criteria

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

1. Subjects with non-cutaneous melanoma (eg, of uveal/ocular or mucosal origin)
2. Subjects with acral melanoma
3. Subject had disease progression as BOR to prior PD-1/PD-L1 containing regimen in the metastatic setting.
4. Subject has been exposed to any of the following prior therapies/treatments within the specified timeframes:
    a. Prior exposure to agents directed at costimulatory T-cell receptors (eg, 4-1BB, OX40)
    b. Treatment with an anticancer agent within 28 days or 5 half-lives, whichever is shorter, prior to the first dose of trial treatment.
    c. Any investigational agent (including investigational vaccines) or used an invasive investigational medical device within 28 days before the planned first dose of trial treatment or is currently enrolled in an interventional trial.

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

d. Prior treatment with live, attenuated vaccines within 30 days prior to initiation of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. Experimental and/or nonauthorized SARS-CoV-2 vaccines as well as live or attenuated SARS-CoV2 vaccines are not allowed.

e. Radiotherapy within 14 days prior to first dose of trial treatment or prior lung radiation therapy of >30 Gy within 6 months of the first dose of trial treatment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids such as prednisone at doses >10 mg daily (or equivalent), and not have had radiation pneumonitis.

   NOTE: Palliative radiotherapy of bone metastases up to 7 days prior to Cycle 1 Day 1 will be allowed. Irradiated lesions cannot be used for efficacy assessment.

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

g. Received G-CSF or granulocyte/macrophage-CSF support within 4 weeks prior to the first dose of trial treatment or being chronically transfusion dependent.

5. Subjects has a known history of any of the following:

   a. Any Grade ≥ 3 irAEs that led to treatment discontinuation of a prior immunotherapy treatment.

   b. Any Grade ≥ 2 event of immune-mediated liver toxicity on prior immunotherapy that did not resolve or return to Grade 1/baseline within 14 days despite immunosuppressive treatment.

   c. Myositis, Guillain-Barré syndrome, or myasthenia gravis of any grade.

   d. Presence or history of noncancerous liver disease (eg, alcoholic hepatitis or nonalcoholic steatohepatitis, drug-related or autoimmune hepatitis, or evidence of hepatic cirrhosis).

   e. Organ allograft (except for corneal transplant) or autologous or allogeneic bone marrow transplant, or stem cell rescue within 3 months prior to the first dose of trial treatment.

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

   g. Toxicities from previous anticancer therapies that have not resolved to baseline levels or to Grade ≤ 1, except for alopecia, anorexia, vitiligo, fatigue, hyperthyroidism, and hypothyroidism. Anorexia, hyperthyroidism, and hypothyroidism must have recovered to Grade ≤ 2.

h. Non-infectious pneumonitis/interstitial lung disease requiring systemic steroids within the last 6 months or ongoing pneumonitis/interstitial lung disease at baseline.

6. Subject has known past or current malignancy other than inclusion diagnosis, except for nonmelanoma skin cancers; in situ cancers of bladder, gastric, colon, cervical/dysplasia, endometrial, melanoma, breast or localized prostate cancer (subjects with very low and low risk prostate cancer qualifying for active surveillance per NCCN or similar guidelines); and any curable cancer with a complete response of >2 years duration that does not require or is not anticipated to require any additional therapy. Subjects with ongoing hematological (pre)malignancies are also excluded from the trial.
7. Has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain) in the opinion of the treating investigator.
8. All subjects should undergo MRI scan of the brain to document new or existing CNS lesions (CT scan is only allowed as an exception with written agreement with sponsor's medical monitor). Subjects with history of intracerebral arteriovenous malformation, cerebral aneurysm, progressing brain metastases, spinal cord compression (from disease), or stroke (within the last 6 months) will be excluded.

   NOTE: History of transient ischemic attack >1 month prior to screening is allowed.
9. Subjects with newly identified or known unstable or symptomatic CNS metastases or history of carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression) for at least 28 days by repeat imaging (note that the repeat imaging should be performed during trial screening). Subjects should be clinically stable and should not be undergoing acute corticosteroid therapy or steroid taper or have received stereotactic radiation or whole-brain radiation within 14 days prior to Cycle 1 Day 1. Chronic steroid therapy is acceptable provided that the dose is stable for at least 14 days prior to Cycle 1 Day 1 (≤ 10 mg prednisone daily or equivalent).
10. Has known allergies, hypersensitivity, or intolerance to acasunlimab or pembrolizumab or their excipients.
11. Has contraindications to the use of pembrolizumab per local prescribing information.
12. Is a female who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this trial or within 4 months after the last dose of trial treatment.
13. Has uncontrolled intercurrent illness or condition that could affect compliance with the protocol or interpretation of the results, including but not limited to:
    a. Ongoing or active infection requiring IV treatment with anti-infective therapy that has been administered < 2 weeks prior to first dose or any ongoing systemic inflammatory condition requiring further diagnostic workup or management during screening.
    b. Symptomatic congestive heart failure (Grade 3 or 4 as classified by the New York Heart Association), unstable angina pectoris, or cardiac arrhythmia.

       NOTE: Myocardial infarction > 6 months prior to screening is allowed.
    c. Uncontrolled hypertension defined as systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 100 mmHg, despite optimal medical management.

d. Uncontrolled diabetes defined as fasting plasma glucose > 250 mg/dl or HbA1c > 8% or symptoms of hyperglycemia, despite optimal medical management.

e. Ongoing or recent (within 6 months) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for irAEs.

   NOTE: Residual hypothyroidism that required only hormone replacement is not exclusionary.

f. Ongoing Grade ≥ 2 sensory or motor neuropathy.

g. Serious, non-healing wound, skin ulcer, or bone fracture.

h. Substance abuse, medical, psychological, or social conditions that may interfere with the subject's participation in the trial or evaluation of the trial results.

14. Has any health condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments. Additionally, vulnerable subjects or subjects under guardianship, curatorship, judicial protection or deprived of liberty, are excluded from participation in this trial.

15. Subject has had major surgery (eg, requiring extended recovery period) within 28 days before Cycle 1 Day 1, or will not have fully recovered from surgery, or has major surgery planned during the time the subject is expected to participate in the trial (or within 28 days after the last dose of trial treatment).

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

16. Has a known history of seropositivity for HIV

    Note: HIV testing is required at screening only if required per local health authorities or institutional standards.

17. Hepatitis B or C:

    a. HBV: Positive serology for HBV (defined as positive for HBsAg) or detection of HBV DNA.

       NOTE: Subjects with a prior HBV infection (HBsAg negative, HBV DNA negative, but anti-HBc positive) can be included if they receive HBV prophylactic antiviral therapy.

    b. HCV: Positive for HCV RNA

    NOTE: Subjects who have active HBV (DNA PCR-positive) or HCV (RNA PCR-positive) infection, current alcohol abuse, or cirrhosis are excluded. Subjects who received treatment for HCV that was intended to eradicate the virus may participate if HCV RNA levels are undetectable.

18. Country-specific exclusion:

    19FR: France: See Section 10.7.2 for requirements per local health authorities.

5.3 Subject Enrollment

A subject is considered enrolled after they have been randomized.

Each subject who enters into the screening period for the trial (defined as when the subject signs the informed consent) receives a unique subject identification number before any trial-related activities/procedures are performed. The subject identification number will be assigned by IRT. This number will be used to identify the subject throughout the clinical trial and must be used on all trial documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical trial; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the trial.

5.4 Screen Failures

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

Individuals who screen failure may be rescreened 1-time following consultation with the sponsor medical monitor. All eligibility criteria must be reassessed (including obtaining consent) at the rescreening visit (refer to Section 10.1.6 for ICF process regarding rescreening). Previous informed consent and screening assessments (eg, scans, certain labs, ePRO) may be used for rescreening purposes if still considered to be within the protocol-required window for the new planned date of Cycle 1 Day 1 as indicated in the Schedule of Activities (Section 1.3). Scans that exceed the 28-day window may be used for trial enrollment after discussion with the sponsor

Laboratory assessments that did not meet the criteria for participation in this trial and that fell outside of the allowed screening window need to be repeated for rescreening (refer to Section 10.1.6 for ICF process regarding rescreening).

6 TRIAL TREATMENT

6.1 Investigational and Auxiliary Medicinal Product(s)

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).

Trial treatment should be administered as described in Table 6 and Table 7 until 1 or more of the discontinuation criteria in Section 7 are met.

Detailed dose modification guidance is provided in Section 6.7. Information regarding concomitant therapy is provided in Section 6.7.1. For additional guidance on trial drug, refer to the IMP Manual.

Table 6: Investigational Medicinal Product(s)

Trial Drug Name	Acasunlimab[a,b]	Pembrolizumab[a,b]
Dosage Formulation	Concentrate for solution for infusion	Concentrate for solution for infusion
Dose (including schedule and cycle length)	100 mg Q6W (42-day cycles)	400 mg Q6W (42-day cycles)
Route of Administration	IV	IV
Dosing Instructions	Administered over 30 minutes. Refer to the IMP Manual for detailed instructions including drug dilution and injection volume.	Pembrolizumab will be administered first over 30 minutes and must be promptly followed by a saline flush to clear the line before starting the infusion of acasunlimab. The time in between infusions should be 30 minutes or longer depending on the situation. Refer to the IMP Manual for detailed instructions including drug dilution and injection volume.
Hospitalization/ Monitoring Guidance	As a routine precaution, all subjects must be observed on Day 1 of Cycle 1 and Cycle 2 for at least 2 hours after ending infusion of acasunlimab. If there were no post-infusion AE(s), for all subsequent cycles subjects must be observed for at least 1 hour after ending infusion of acasunlimab. Subjects must be observed in an area with facilities, equipment, and staff that allow immediate medical intervention in case urgent or critical medical support is needed. At all times during acasunlimab infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation. All guidance should be followed from the protocol and as per local guidelines. Additional and prolonged monitoring of subject safety during treatment administration may be implemented per investigator's discretion. As data	

Trial Drug Name	Acasunlimab[a,b]	Pembrolizumab[a,b]
	accumulate, increased (or reduced) monitoring may be implemented for additional dose administrations if recommended by the sponsor.	
Packaging	Acasunlimab will be provided in a glass vial containing 5 mL [redacted].	Pembrolizumab will be provided in a glass vial containing 4 mL (25 mg/mL).
Labeling	Trial drug labels will contain information to meet the applicable regulatory requirements. For further details see the IMP Manual.	

Abbreviations: AE=adverse event; IMP=investigational medicinal product
[a] Refer to the IMP Manual for further details.
[b] Refer to Section 10.7.1 for EU authorisation status.

Table 7: Auxiliary Medicinal Products

AMP Name	**Dexamethasone or methylprednisolone or prednisone (or equivalent)**[a]
Use	1. Reactive premedication to mitigate irAEs 2. Management of immune-related hepatitis
Dosage/frequency	1. Reactive steroid premedication to prevent irAE if episodes occurred with previous cycles of trial drug: Prednisone 10 mg daily (or equivalent) for at least 10 days 2. Steroid management of immune-mediated hepatitis Initial dose of 0.5-2 mg/kg methylprednisolone or equivalent until Grade ≤ 1
Route of administration	IV or oral
Dosing instructions	See Section 6.7.1.2.1, Section 6.7.1.3, Section 10.9, Section 10.11, and Table 8
Packaging and labelling	Not applicable, as sites will source, unless it is agreed the sponsor will provide the drug. If AMP is sourced centrally, labels will contain information to meet the applicable regulatory requirements.

Abbreviations: AMP= auxiliary medicinal product; irAE=immune-related adverse event; IV=intravenous
[a] Refer to Section 10.7.1 for EU authorization status.

6.2 Product Complaints

A product complaint is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A complaint may have an impact on the safety and efficacy of the product.

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

In addition to reporting the complaint, if the product defect is combined with an AE or SAE, the trial-site personnel must report the AE or SAE to the sponsor according to the AE and SAE reporting process and timelines (refer to Section 8.4.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Preparation, Handling, and Storage

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

6.3.2 Drug Accountability and Destruction

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

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

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

6.4 Measures to Minimize Bias: Randomization and Blinding

6.4.1 Treatment Assignment

This is an open-label trial.

Subjects will be assigned to treatment arms by the IRT system. Refer to the IRT user guide for additional information and stepwise guidance on enrollment procedures.

Randomization will be used to avoid bias in the assignment of subjects to treatment arms and to ensure the validity of statistical comparisons across treatment arms.

Randomization will occur centrally using an IRT system. Randomization must occur ≤ 3 days prior to dosing. There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to acasunlimab 100 mg Q6W + pembrolizumab 400 mg Q6W (Arm A) or acasunlimab 100 mg Q6W (Arm B).

The randomization will be balanced using randomly permuted blocks and will be stratified by:

- BRAF V600 mutational status: wild type vs mutant
- LDH levels: ≤ ULN vs > ULN

6.5 Treatment Compliance

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

Treatment start and stop dates, including dates for trial drug delays will also be documented.

Treatment dosing interruptions will be recorded, including the timing of the interruption and restart, eg, for situations where IRRs occur during infusion of IMP.

6.6 Prior and Concomitant Therapies

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

6.6.1 Prior Therapies

Prior anticancer therapies received from the time of initial diagnosis and until 28 days before administration of the first dose of trial drug for the treatment of cutaneous melanoma in the neoadjuvant, adjuvant, and/or metastatic setting (including surgery, radiotherapy, chemoradiotherapy, systemic treatment regimens, etc) must be documented.

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

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

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

6.6.2 Prophylactic Vaccines

It is strongly recommended that subjects are up to date on prophylactic vaccines prior to enrollment, including but not limited to seasonal vaccines (COVID-19, influenza, RSV) as well as age- and risk-based vaccines (herpes zoster, pneumococcal, Tdap) adhering to ASCO (Kamboj et al., 2024), NCCN (Rodriguez, 2022), and relevant local guidelines by national health agencies. Vaccination with non-live vaccines should be performed at least 2 weeks prior to Cycle 1 Day 1. Note: live, attenuated vaccines (eg, nasal spray influenza vaccines, MMR, varicella) are not allowed within 30 days prior to enrollment.

Prior to enrollment, subjects should provide information on the type and timing (date) of all vaccines received in the last 6 months prior to Cycle 1 Day 1, if known, and this information should be appropriately entered in the eCRF.

6.6.2.1 Recommended Prophylactic Vaccinations for Adult Subjects With Cancer

COVID-19 vaccine

Following the ASCO guidelines (Kamboj et al., 2024), if the last COVID-19 vaccine dose was ≥ 2 months prior and the subject did not have a COVID-19 infection in the last 2-3 months, it is strongly recommended to administer a COVID-19 vaccine booster during the Screening period for all subjects, at least 2 weeks prior to Cycle 1 Day 1. This is to prevent COVID-19 infection during the trial which can lead to hospitalization and/or require dose delays. Furthermore, the vaccine booster may offer an additional benefit by expanding and stimulating the pre-existing T-cell pool and enhancing T-cell homing to tumor sites (Middelburg et al., 2024), which may improve the clinical response to subsequent trial drug. COVID-19 mRNA-based vaccine boosters are recommended over adenoviral-based and protein subunit-based boosters.

Influenza vaccine

Seasonal influenza vaccine is recommended annually for all subjects, ideally to be administered by the early fall in the northern hemisphere. It is recommended that subjects aged 65 years or older receive the high-dose or adjuvanted vaccine formulations (high-dose Quadrivalent vaccine, Quadrivalent recombinant flu vaccine, and Quadrivalent adjuvanted flu vaccine). The influenza vaccine can be co-administered with the COVID-19 vaccine booster.

RSV vaccine

The RSV vaccine is recommended as one-time administration for subjects with cancer aged 60 years or older. The vaccine can be co-administered with other seasonal vaccinations.

Tdap or Td vaccine

Administration of a Tdap vaccine is strongly recommended for subjects with cancer if they did not receive the vaccine as adults (19 years or older). The initial dose of Tdap should be followed by Tdap or Td booster every 10 years.

Recombinant zoster vaccine

The adjuvanted RZV is recommended for subjects with cancer aged 19 years or older. Two vaccine doses, at least 4 weeks apart, should be administered for optimum protection.

Pneumococcal vaccines

The pneumococcal vaccines are recommended for subjects with cancer aged 19 years or older. Adult subjects with cancer who have not been vaccinated before can either receive 1 dose of the pneumococcal conjugate vaccine PCV20 or 1 dose of PCV15 followed by 1 dose of the pneumococcal polysaccharide vaccine PPSV23 administered at least 8 weeks apart. For subjects previously vaccinated with PCV13 only, 1 dose of PCV20 is recommended after a period of 1 year.

Hepatitis B vaccine

For subjects with cancer without prior immunity to hepatitis B, vaccination is recommended for adults aged 19 to 59 years and those 60 years or older with other risk factors (HIV, chronic liver diseases, IV drug use, sexual risk factors, incarcerated individuals). For adults 20 years or older, the high antigen (40 µg) vaccine formulation is recommended, which

includes either the 3-dose Recombivax HB series (0, 1, 6 months) or 4-dose Engerix-B series (0, 1, 2, 6 months).

Other recommended prophylactic vaccines

For additional prophylactic vaccine recommendations that may be indicated for adult subjects with cancer with co-existing health conditions and/or subjects who may not have had all recommended childhood vaccines, please refer to the ASCO guidelines (Kamboj et al., 2024).

6.6.3 Concomitant Therapies

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

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

Following the 90-day safety follow-up visit, subsequent anticancer therapy will continue to be collected. Concomitant therapies should also be documented beyond 90 days after the last dose of trial treatment only for new SAEs related to trial treatment. Refer to Section 8.4.6 for additional information regarding follow-up AEs and SAEs.

6.6.3.1 Permitted Concomitant 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 nonreplicating viral vector-based vaccines. Consider choosing an appropriate type of SARS-CoV-2 vaccine and consult with an infectious disease expert if desired.
- Steroid treatment is permitted as reactive premedication to acasunlimab treatment and to modulate symptoms, eg, of an irAE, at the discretion of the investigator (see Section 6.7.1.3). Corticosteroids for topical or ocular use; for intraarticular joint use; or for inhalation in the management of asthma or chronic obstructive pulmonary disease are allowed.
- Palliative radiotherapy during the trial will be allowed for local pain control provided that:
  - in the opinion of the investigator, the subject does not have progressive disease, AND
  - no more than 10% of the subject's bone marrow is irradiated, AND
  - the radiation field does not encompass a target lesion
  - NOTE: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- G-CSF and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia and Grade ≥ 3 neutropenia, when clinically

indicated or at the investigator's discretion. In case of recurring Grade ≥ 3 neutropenia, use of growth factors is mandated.

NOTE: G-CSF or other hematopoietic growth factors (eg, granulocyte/macrophage colony stimulating factor) are not allowed within 4 weeks prior to the first dose of trial drug.

- Prophylactic antibiotics are also permitted per institutional standard practice.
- Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency)
- Bisphosphonates (eg, pamidronate, zoledronic acid, etc) and denosumab
- RBC and platelet transfusions, if clinically indicated

  NOTE: Subject must not be chronically transfusion dependent for at least 4 weeks prior to trial entry. RBC transfusion is not allowed within 4 weeks prior to the first dose of trial drug.
- Multivitamins, vitamin D, calcium, and supplements for prevention of weight loss
- Prescribed medicinal cannabinoids as palliative therapy

6.6.3.2 Prohibited Concomitant Therapies

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

The following concomitant therapies are prohibited from Cycle 1 Day 1 until 90 days after last dose of trial treatment:

- Any other investigational therapy
- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Radiation therapy, unless for palliative purposes (see Section 6.6.3.1)
- Immunotherapy not specified in the protocol
- Chronic systemic immunosuppressive corticosteroid doses (ie, prednisone > 10 mg daily or equivalent) or steroid treatment for any other purpose than to manage emergency situations (according to institutional standards), reactive premedication to acasunlimab or corticosteroids to manage an irAE or IRR (Section 6.7.1.3).
- Live, attenuated vaccines while participating in the trial and for 90 days following the last dose of trial treatment
- No dietary supplements are allowed during the trial period (except for multivitamins, vitamin D, calcium, and supplements in prevention of weight loss), without first consulting with the investigator.
- The use of herbal medicines is not permitted.

6.7 Dose Modification and Discontinuation

6.7.1 Dose Modification Guidance and Discontinuation Criteria for Acasunlimab and Pembrolizumab

Decisions regarding dose modification of the trial drugs should be based on clinical judgment, taking into account the relatedness of the AE to the trial drugs, the subject's underlying condition, and any other relevant circumstances. Acasunlimab and pembrolizumab are considered immune modulators and AEs associated with these compounds may have an immunologic etiology (ie, irAEs), which is defined as an AE consistent with an immune phenomenon associated with drug exposure after all other etiologies have been eliminated.

6.7.1.1 Dose Reductions

No dose modification (increase or decrease) of acasunlimab or pembrolizumab will be permitted for this trial; however, a dose of acasunlimab and pembrolizumab may be omitted or delayed for single cycles only if considered appropriate by the investigator, see below and Table 8.

6.7.1.2 Dose Delays

Dose delays relate to the postponement of subsequent infusion of trial drug.

If acasunlimab and pembrolizumab are delayed > 12 weeks, the subject must be permanently discontinued from treatment with the following exceptions that may be allowed with agreement from the sponsor's medical monitor:

- Dosing delays to allow for prolonged steroid tapers (ie, ≤ 10 mg prednisone [or equivalent] per day) to manage treatment-related AEs
- Dosing delays > 12 weeks that occur for nontreatment-related reasons

Tumor assessments should continue as per protocol even if dosing is delayed.

When treatment resumes in Arm A, both acasunlimab and pembrolizumab must be started together. If pembrolizumab is permanently discontinued due to safety issues, acasunlimab may be restarted as monotherapy after discussion with the Sponsor. For this trial, dosing interruption refers to any interruption of the trial drug infusion to support the management of acute toxicity related to administration of trial drug, eg, to manage IRRs. The timing and duration of interruption should be recorded.

6.7.1.2.1 Immune-Related Adverse Events

AEs associated with the combination of acasunlimab and pembrolizumab may have an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of these treatments 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 for acasunlimab and the prescribing information for pembrolizumab, irAEs in this trial are generally expected to be reversible and managed with drug delays, administration of corticosteroids, and/or other supportive care.

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 acasunlimab alone, or to pembrolizumab alone, for AEs listed in Table 8, both acasunlimab and pembrolizumab must be held until resolution of the AEs according to the criteria in Table 8.

General Instructions:

- Depending on the severity of irAEs, acasunlimab and pembrolizumab should be withheld or permanently discontinued, and corticosteroids administered, according to Table 8.
- For severe and life-threatening irAEs, an IV corticosteroid should be initiated immediately (under hospital admission). Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids. See Table 8 for more detailed instructions.
- It is important to exclude infections diligently at admission and to keep monitoring the subject closely (eg, with vital signs, hematology, LFTs, procalcitonin, and inflammatory markers, including CRP and ferritin) on (at least) a daily basis to exclude potential new infections. Infections should be treated immediately and adequately per the local SOC. In addition to following the recommendations in Table 8, trial drug should also be withheld until infection has resolved.
- If a subject is receiving high-dose corticosteroids (eg, ≥ 2 mg/kg for ≥ 3 days), initiate broad spectrum antibiotics covering nosocomial infections as well as antifungals (unless there are contraindications) due to the increased risk of infections during immunosuppression. Concurrent neutropenia may increase the risk of infection.
- Samples for cytokines/soluble factors analysis to be collected as soon as a serious or Grade ≥ 3 irAE (including, but not limited to, ALT/AST elevation, CRS, HLH) is suspected.
- Corticosteroid taper should be initiated for corticosteroid treatment doses of 0.5 mg/kg or higher upon irAE improving to Grade 1 or lower and continue to taper over at least 4 weeks.
- CCI [redacted]
- CCI [redacted]
- Acasunlimab or acasunlimab and pembrolizumab should be permanently discontinued:
  - If the irAE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone (or equivalent) per day.
  - For any recurrence of Grade ≥ 3 irAE with the exception of hypothyroidism.

Refer to Table 8 for additional guidance on the recommended management of irAEs associated with acasunlimab and pembrolizumab. For more information regarding the management of all other irAEs, refer to (Schneider et al., 2021).

Table 8: Dose Modification and Toxicity Management Guidelines for irAEs (Acasunlimab and Pembrolizumab)

irAEs	Toxicity Grade	Action With Pembrolizumab and Acasunlimab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Pneumonitis	Grade 1	Consider withholding treatment or proceed with close monitoring.	None	Monitor for signs and symptoms of pneumonitis. Evaluate with radiographic imaging as needed.
	Grade 2	Withhold treatment until resolution to Grade ≤ 1 and corticosteroid has been tapered.	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper. Add prophylactic antibiotics.	
	Recurrent Grade 2, Grade 3, or Grade 4	Permanently discontinue.		
Diarrhea/colitis	Grade 1	Continue treatment. Alternatively, consider withholding treatment temporarily and resume if toxicity does not exceed Grade 1 or resolves.	Include supportive care with medications such as loperamide if infection has been ruled out in subjects with diarrhea only and not colitis-related symptoms.	Monitor dehydration and recommend dietary changes. Subject should be closely monitored by telephone for symptom changes every 3 days or more frequently if needed until stabilized. Consider gastroenterologist consultation for prolonged Grade 1 cases and endoscopy with biopsies depending on clinical evolution.

irAEs	Toxicity Grade	Action With Pembrolizumab and Acasunlimab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
Diarrhea/colitis (continued)	Grade 2 or 3	Withhold treatment until resolution to Grade ≤ 1 and corticosteroid has been tapered.	May also include supportive care with medications such as loperamide if infection has been ruled out in subjects with diarrhea only and not colitis-related symptoms as a temporary measure. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent) followed by taper. Consider adding narrower-spectrum or more potent agents, including infliximab or vedolizumab to subjects whose colitis is corticosteroid-refractory (ie, no decrease by one grade in 72 hours) or with high-risk endoscopic features on initial endoscopy examination. ***NOTE: infliximab is contraindicated in case of concurrent hepatic irAE.***	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. 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). Gastroenterologist consultation and endoscopy are highly recommended to rule out colitis and for early treatment with biologics based on the endoscopic findings. Consider testing for fecal lactoferrin to determine who needs more urgent endoscopy and calprotectin to follow up on disease activity.
	Recurrent Grade 3 or Grade 4	Follow Grades 2 to 3 recommendations as listed, with the following additions for Grade 4: Permanently discontinue. Should provide inpatient care.	Administer 1 to 2 mg/kg/day methylprednisolone or equivalent until symptoms improve to Grade 1, and then start taper over 4 to 6 weeks. Consider early infliximab or vedolizumab if inadequate response to steroids after 3 days. ***NOTE: infliximab is contraindicated in case of concurrent hepatic irAE.***	Consider lower GI endoscopy if symptoms are refractory, despite treatment or there is concern of new infections.
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irAEs	Toxicity Grade	Action With Pembrolizumab and Acasunlimab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
CCI				

irAEs	Toxicity Grade	Action With Pembrolizumab and Acasunlimab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
	CCI			
T1DM or hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β cell failure	Withhold until glucose control[a].	Initiate insulin replacement therapy for subjects with T1DM. Administer antihyperglycemic treatment in subjects with hyperglycemia.	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes. Endocrine consultation.
Hypophysitis	Grade 1 and Grade 2	Consider withholding until subject is stabilized on replacement hormones.	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Endocrine consultation.
	Grade 3 or 4	Withhold or permanently discontinue[a].		
Hyperthyroidism	Grade 1	Continue.	Treat with nonselective beta blockers (eg, atenolol, propranolol) as appropriate.	Monitor for signs and symptoms of thyroid disorders. Endocrine consultation.
	Grade 2	Continue.	Treat with nonselective beta blockers (eg, atenolol, propranolol) or thionamides as appropriate.	
	Grade 3 or 4	Withhold or permanently discontinue[a].		
Hypothyroidism	Grade 1	Continue treatment with monitoring of TSH.	None	Monitor for signs and symptoms of thyroid disorders.

irAEs	Toxicity Grade	Action With Pembrolizumab and Acasunlimab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
	Grade 2, 3, or 4	Withhold treatment until symptoms resolve to baseline.	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per SOC.	Monitor for signs and symptoms of thyroid disorders. Endocrine consultation.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold treatment until resolved to Grade $\leq$ 1.	Administer corticosteroids (prednisone 0.5-1 mg/kg/day or equivalent) followed by taper.	Monitor changes of renal function. Nephrology consultation.
	Grade 3 or 4	Permanently discontinue.	Administer corticosteroids (prednisone 1 to 2 mg/kg/day or equivalent) followed by taper.	
Neurological toxicities	Grade 2	Withhold.	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes. Neurology consultation
	Grade 3 or 4	Permanently discontinue.		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold treatment for Grade 1 elevated troponin and recheck troponin 6 hours later. May consider resuming once normalized or if believed not to be related to treatment.	For subjects with Grade $\geq$2, early (ie, within 24 hours) initiation of high-dose corticosteroids (1 to 2 mg/kg/day of prednisone, oral or IV depending on symptoms).	All grades warrant workup and intervention, given the potential for cardiac compromise. Ensure adequate evaluation by a cardiologist to confirm etiology and/or exclude other causes. Management of cardiac symptoms according to ACC/AHA guidelines or local clinical practices and with guidance from cardiology.
	Grade 2, 3, or 4	Permanently discontinue.		
Skin toxicities	Grade 1 or 2	Continue treatment at the discretion of the investigator.	Based on severity of the skin toxicity, consider administration of corticosteroids. Corticosteroid taper should be initiated upon irAE improving to Grade 1. For signs and symptoms of Stevens-Johnson syndrome or toxic epidermal necrolysis, withhold and refer to specialized care. Permanently discontinue if diagnosis is confirmed.	Ensure adequate evaluation to confirm etiology or exclude other causes. Dermatology consultation.
	Grade 3	Withhold treatment until resolved to Grade $\leq$ 1.		
	Grade 4	Permanently discontinue.		
Thrombocytopenia	Grade 2	Withhold treatment until resolution to Grade $\leq$1.	Administer prednisone 0.5 to 1 mg/kg/day orally for 4 weeks followed by taper over 4 to 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.	Diagnostic workup. History of autoimmunity. CBC, peripheral blood smear, and reticulocyte count.

irAEs	Toxicity Grade	Action With Pembrolizumab and Acasunlimab	Corticosteroid and/or Other Therapies	Monitoring and Follow-Up
	Grade 3 or 4	Withhold treatment until resolution to Grade ≤1.	Administer methylprednisolone 1 g IV daily for 3 days. If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. If previous use of corticosteroids and IVIG has been unsuccessful, subsequent therapy may include rituximab, thrombopoietin receptor agonists, or more potent immune suppression.	HIV, HCV, HBV, and H. pylori testing. Direct antigen test. Bone marrow evaluation if other cell lines affected and concern for aplastic anemia. Hematology consultation.
Neutropenia and febrile neutropenia	Neutropenia: Grade 3 or first occurrence of Grade 4	Hold dosing until event has improved to Grade ≤ 1.	Administer colony-stimulating factors including G-CSF, pegylated G-CSF, or GM-CSF according to institutional guidance.	Diagnostic workup: CBC with differential and blood smear evaluation. Monitor closely for infections. Concurrent neutropenia and treatment with high-dose corticosteroids may increase the risk of infections. Consider adding prophylactic broad-spectrum antibiotics and antifungals.
	Neutropenia: second occurrence of Grade 4	Hold dosing until event has improved to Grade ≤ 1. Discuss with sponsor the discontinuation of treatment.		
	Febrile neutropenia: any grade	Hold dosing until fever has resolved.	Administer colony-stimulating factors including G-CSF, pegylated G-CSF, or GM-CSF according to institutional guidance. Use of antibiotics according to the results of the culture and local guidelines.	A complete infectious workup must be done prior to resuming trial drug. This infectious workup should include blood cultures, urinalysis, urine culture, and chest X-ray. Inpatient admission and hematology consultation should be considered, if deemed appropriate by the investigator. If infection is confirmed, treat with antibiotics and withhold trial drug until resolution of both infection and neutropenia.
All other irAEs[b]	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.		

Abbreviations: ACC=American College of Cardiology; AE=adverse event; AHA=American Heart Association; ALT=alanine transaminase; ASCO=American Society of Clinical Oncology; AST=aspartate transaminase; CBC=complete blood count; CRP=C-reactive protein; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; G-CSF=granulocyte colony stimulating factor; GI=gastrointestinal; GM-CSF=granulocyte-macrophage colony-stimulating factor; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human

immunodeficiency virus; HLH=hemophagocytic lymphohistiocytosis; irAE=immune-related adverse event; IV=intravenous(ly); IVIG=intravenous immunoglobulin; SOC=standard of care; T1DM=type 1 diabetes mellitus; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

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

[a] The decision to withhold or permanently discontinue pembrolizumab and/or acasunlimab is at the discretion of the investigator or treating physician. If control achieved or Grade ≤ 2, pembrolizumab and/or acasunlimab may be resumed.

[b] Refer to Section 6.7.1.2.2 for guidance regarding hyperinflammatory syndromes (CRS and HLH). *Refer to Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update* (Schneider et al., 2021) for more information regarding management of all other irAEs.

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

6.7.1.2.1.1 Resuming Trial Drug After Grade 3 Immune-Mediated Hepatitis Event

Resuming pembrolizumab and/or acasunlimab for subjects who have recovered from a Grade 3 hepatic irAE may be considered if the following criteria are met (following discussion with the sponsor medical monitor and written agreement is documented):

- The event of Grade 3 AST/ALT elevation was asymptomatic
- The event responded to corticosteroid therapy and resolved or returned to Grade 1 or baseline within 14 days
- New scan confirms continued clinical benefit (SD or better response)
- Investigator commitment to undertake close monitoring including collection of LFTs at least twice a week for the first 3 weeks after treatment has been resumed, then once weekly for 3 weeks after the subsequent dose of pembrolizumab and/or acasunlimab

6.7.1.2.2 Hyperinflammatory Syndromes

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

6.7.1.2.2.1 Cytokine Release Syndrome

Any event of CRS should be graded according to ASTCT criteria described by (Lee et al., 2019) and in Section 10.9.

Trial drug should be permanently discontinued for subjects with Grade ≥ 3 CRS (except for Grade 3 CRS which has improved to Grade 1 or resolved within 72 hours). However, per protocol, subjects should continue safety follow-up until the subject withdraws from the trial or starts another course of systemic anticancer therapy.

Management of CRS should follow the established guideline (Varadarajan et al., 2020) or local SOC, with supportive treatment controlling fever, hypotension, and hypoxia; and in more severe cases, with anti-IL-6R mAb (eg, tocilizumab or equivalent), systemic steroids, and vasopressors. See Section 10.9.

6.7.1.2.2.2 Hemophagocytic Lymphohistiocytosis

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

Hyperferritinemia should always prompt inclusion of HLH as differential diagnosis. If ferritin levels are increased above 500 µg/L, they should be monitored closely. Ferritin values characteristic of HLH in adults are often > 7000 µg/L. However, any rapid increase in the ferritin level compared to baseline per clinical assessment should raise the index of suspicion (Hines et al., 2023). If HLH is suspected, elevated soluble IL-2 receptor (sCD25) has been reported as a diagnostic test for adult HLH and it is recommended to assess sCD25 locally (per local standard) together with fibrinogen, triglycerides, and D-dimer. Other features supporting an HLH diagnosis that are not part of the HLH-2004 criteria below include elevated liver transaminases, hyperbilirubinemia, hepatomegaly, and elevated LDH (La Rosée et al., 2019).

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

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

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

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

Any event of HLH should be graded according to immune effector cell-associated HLH-like syndrome grading (Hines et al., 2023) (Section 10.10). The management of HLH should be tailored to control hyperinflammation and to treat identified disease triggers. Treatment with high-dose corticosteroids (start dose 2 mg/kg IV) is the cornerstone of treatment. Early intervention with high-dose steroids alone may be successful in the treatment of HLH induced by immune checkpoint blockade (Sadaat and Jang, 2018; Takahashi et al., 2020). If no reversal of laboratory parameters (including ferritin and bilirubin increases) within 24 hours, pulsed corticosteroids, eg, 1000 mg/day for 3 days according to (Takahashi et al., 2020), should be initiated immediately. If no improvement within 24 to 48 hours from the initiation of corticosteroid pulse therapy, treatment with anakinra or JAK1/2 inhibitors should be added (Hines et al., 2023; Keenan et al., 2021). For refractory cases, etoposide (an element of the HLH-94 protocol) may be used. Dose and frequency adjustments are advised for adult subjects (La Rosée et al., 2019).

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6.7.1.3 Infusion-Related Reactions to Acasunlimab

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

- Grade 1:
  - If an IRR of 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 or 3:
  - If a Grade 2 or 3 IRR occurs, the infusion should be interrupted, and appropriate medical management instituted. The infusion may be restarted at the investigator's discretion at half the infusion rate under close medical supervision if symptoms have resolved to Grade $\leq$ 1 within 1 hour.
  - Subjects who have experienced prior Grade 2 or 3 IRRs in the trial should be premedicated. Premedication to prevent IRRs in subsequent infusions may be administered at the investigator's discretion according to local guidelines but preferably should include 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. Administration of corticosteroids as premedication will require prior written approval from the sponsor's medical monitor.
  - If the subject has a second Grade 3 IRR despite premedication, administration of acasunlimab and pembrolizumab should be discontinued immediately and permanently, and appropriate medical therapy should be administered.

- Grade 4:
  - If anaphylaxis or Grade 4 IRR occurs, administration of acasunlimab and pembrolizumab should be discontinued immediately and permanently, and appropriate medical therapy should be administered.

NOTE:

- As a routine precaution, all subjects must be observed on Day 1 during Cycle 1 and Cycle 2 for at least 2 hours after ending infusion of acasunlimab. If there were no post-infusion AEs, for all subsequent cycles, subjects must be observed for at least 1 hour after ending infusion of acasunlimab.
- Subjects must be observed in an area with resuscitation equipment and emergency agents.
- At all times during acasunlimab infusion, immediate emergency treatment of an anaphylactic reaction according to institutional standards must be assured. In order to treat possible anaphylactic reactions, dexamethasone 10 mg and epinephrine in a 1:1000 dilution or equivalents should always be available along with equipment for assisted ventilation.
- All premedication(s) must be reported on the concomitant medication page in the eCRF.

6.7.1.4 Infusion-Related Reactions to Pembrolizumab

Pembrolizumab may cause severe or life-threatening IRRs including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab-associated infusion reaction are provided in Table 9.

Table 9: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None

Grade 2
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours
	• **Stop Infusion.**
	• Additional appropriate medical therapy may include but is not limited to:
	  ○ IV fluids
	  ○ antihistamines
	  ○ NSAIDs
	  ○ acetaminophen
	  ○ narcotics
	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.
	• If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hour to 50 mL/hour). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.
	
	Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further causative trial drug treatment.
		Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of trial intervention with:
		• diphenhydramine 50 mg PO (or equivalent dose of antihistamine).
		• acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: o epinephrine[a] o IV fluids o antihistamines o NSAIDs o acetaminophen o narcotics o oxygen o pressors o corticosteroids • Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated.	No subsequent dosing
Grade 4: Life-threatening; pressor or ventilator support indicated	• Subject is permanently discontinued from further causative trial drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of trial drug administration. For further information, please refer to CTCAE v5.0 at http://ctep.cancer.gov.		

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous(ly); NCI=National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drug(s); PO=orally.

[a] In cases of anaphylaxis, epinephrine should be used immediately.

6.7.2 Permanent Discontinuation of Treatment Due to Adverse Events

When acasunlimab is permanently discontinued due to an AE, pembrolizumab will also be permanently discontinued; the subject will be treated as per SOC of the institutional/investigator's discretion. All the end of treatment and post-treatment trial procedures, including efficacy assessments, will be performed following acasunlimab and pembrolizumab discontinuation.

Pembrolizumab can be permanently discontinued due to an AE if the AE can be clearly attributed to pembrolizumab alone. After consultation with the sponsor, acasunlimab may continue to be administered. All trial procedures, including efficacy assessments, will continue to be performed. Subjects move into the safety follow-up period once both drugs have been discontinued.

6.8 Treatment of Overdose

6.8.1 Acasunlimab

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

Sponsor does not recommend specific treatment for an overdose.

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

In the event of an overdose, the investigator should:

- Contact the sponsor's medical director (or delegate) immediately (see Section 8.4.3.2.1).
- Closely monitor the subject for any AE/SAE and laboratory abnormalities
- Consider plasmapheresis, in consultation with the sponsor
- Obtain a blood sample for PK analysis if requested by the sponsor's medical director (or delegate) (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.8.2 Pembrolizumab

An overdose of pembrolizumab is defined as any dose of 1000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Refer to current local pembrolizumab prescribing information for information on treatment of overdose.

6.9 Treatment Beyond Progression

Where subjects are clinically stable and are deemed to derive potential clinical benefit from continued treatment with their assigned trial drug beyond documented radiographic disease

progression according to the treating investigator, the subject may continue to receive their allocated trial drug therapy after discussion with the Sponsor medical monitor and written agreement with the Sponsor is documented. Where acasunlimab has been given in combination with pembrolizumab, the duration of this continued combination therapy must be in line with the duration of therapy as indicated in local guidelines and/or prescribing information for the use of pembrolizumab and provided it is in the best interests of the subject and the subject remains clinically stable. The subject will continue to be evaluated per protocol.

Subjects who require an emergent intervention due to rapid disease progression (eg, CNS metastases requiring immediate treatment) or subjects who have signs or symptoms of clinically significant progression are not eligible for treatment beyond progression.

Subjects who are clinically stable must meet all of the following criteria:

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

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

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

7 DISCONTINUATION OF TREATMENT AND WITHDRAWAL FROM TRIAL

7.1 Discontinuation of Treatment

Subjects can decline to continue receiving trial treatment and/or other protocol-required therapies or procedures at any time during the trial but continue participation in the trial. Subjects who have discontinued trial treatment and/or other protocol-required therapies or procedures should not be automatically removed from the trial. Whenever safe and feasible, it is imperative that subjects remain on-trial to ensure safety surveillance and/or collection of outcome data (ie, continue imaging/efficacy evaluations according to the trial protocol, see Section 8.2).

The subject may discontinue both trial treatment and further participation in trial activities; however, they may continue to be followed for survival (see Section 7.1.2.4) and are not considered discontinued from the trial (see Section 7.2).

7.1.1 Criteria for Permanent Discontinuation of Trial Treatment

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

- Disease progression according to response criteria (Section 8.2.1)
- Clinical progression and/or absence of clinical benefit
- Unacceptable AE(s) leading to treatment discontinuation
  - See general instructions in Section 6.7.1.2.1
- Subject request to discontinue trial treatment
- Sponsor or investigator decision
- Subject noncompliance
- Pregnancy
- Lost to follow up
- Dosing delays > 12 weeks, unless written approval is provided by the sponsor's medical monitor
- Planned medical intervention (eg, surgery) that is likely to delay treatment dosing for ≥ 21 days and/or is unlikely to allow restart of trial drugs, unless written approval is given by the sponsor medical monitor.
- Initiation of new systemic anticancer therapy

7.1.2 Follow-up After Permanent Treatment Discontinuation

7.1.2.1 End of Treatment Visit

The end of treatment visit should be conducted as soon as possible after the decision to end treatment (preferably within 7 days from the date the decision is made by the investigator to discontinue trial treatment) and before the start of new anticancer therapy.

7.1.2.2 Safety Follow-up Visit(s)

Subjects discontinuing from treatment for any reason will have 2 safety follow-up visits 60 days (+5 days; SFU1) and 90 days (±7 days; SFU2) after the subject receives the last dose of trial treatment. If the decision for treatment discontinuation is made at least 55 days after the last dose of trial treatment, the 60-day safety follow-up visit can be combined with the end of treatment visit.

If the subject initiates new anticancer treatment (eg, systemic; radiation/surgery to target lesion) within 90 days of the last dose of trial treatment, the safety follow-up visit should be performed prior to starting new anticancer treatment as indicated in Table 10. No safety follow-up visits should be performed after the initiation of new anticancer treatments.

No monitoring of AEs is required after the safety follow-up visit(s); however, if an investigator becomes aware of a trial treatment-related SAE, this SAE must be reported.

Table 10: Follow-Up Visit Requirements Prior to Initiation of New Anticancer Therapy

Initiation of New Anticancer Therapy	Follow-Up Period Visit Requirements
Within 30 days of final trial treatment	No safety follow-up visit required if initiating new anticancer therapy.
30 to 60 days after final trial treatment	Complete SFU1 prior to initiating new anticancer therapy.
60 to 90 days after final trial treatment	Complete SFU2, unless the SFU1 was completed < 14 days prior to initiating new anticancer therapy.

Abbreviations: SFU=safety follow-up.

The subject will move into survival status follow-up after the safety follow-up visit(s) (see Section 7.1.2.4). Once subsequent anticancer treatment is initiated, the subject will move into survival status follow-up. Where possible, the visits should be conducted in person.

7.1.2.3 Post-Treatment Efficacy and Safety Follow-up Period

Upon permanent discontinuation of trial treatment prior to disease progression and start of new anticancer treatment, post-treatment assessments for safety and efficacy should continue until disease progression or start of new therapy, whichever comes first, as described in the Schedule of Activities (Section 1.3).

7.1.2.4 Survival Status Follow-up Period

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

Site personnel, or an independent third party, will attempt to collect the survival status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not receive trial treatment. Subjects may be contacted by telephone, email, or visit. Additionally, survival status will be collected through medical records, national registries, or

publicly available information as allowed per local regulation. If survival status is determined as deceased, this will be documented.

7.2 Withdrawal From the Trial

Reasons for withdrawal of a subject from the trial may include any of the following:

- Death
- Lost to follow up
- Sponsor decision
- Subject withdrew consent from trial participation

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

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

7.3 Lost to Follow Up

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

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

If a randomized subject is lost to follow-up, every effort should be made by the site to collect survival status information (ie, whether the subject is alive or dead, and date of death) via, for example, medical records or publicly available information.

7.4 Trial Stopping Rules

The trial may be stopped for unacceptable toxicity as per the sponsor's Safety Committee recommendation and based on a risk-benefit assessment.

8 TRIAL ASSESSMENTS AND PROCEDURES

Overview

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

All assessments should be performed prior to trial treatment administration, unless otherwise indicated in the Schedule of Activities. If multiple assessments are scheduled for the same time point, it is recommended that procedures be performed in the following sequence: ECG (baseline and if clinically indicated), vital signs, blood sample collections for PK, biomarkers, safety laboratory tests, and all other laboratory tests. Collections for PK and pharmacodynamic assessments should be kept as close to the specified time as possible.

All PRO assessments (see Section 8.9) should be conducted/completed before any tests, procedures, or other consultations to prevent influencing subject perceptions.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, 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 collected at screening, where permitted by local regulations:

- Gender and sex assigned at birth
- Age at time of screening
- Race
- Ethnicity

Rationale for collecting race and ethnicity in all subjects: Clinical development of a drug requires an understanding of the optimal dose and/or exposure–effect relationship. To understand the relationship between exposure and safety/efficacy, PK of the drug needs to be characterized in a patient population, which includes quantitative characterization of IIV. Specifically, understanding of IIV at the population level can be achieved using population PK modelling, where the PK of a drug is characterized in the target patient population and IIV is investigated by assessing the effect of different covariates on PK parameters. Historically, race and ethnicity are important demographic variables contributing to IIV (Gill et al., 2016; Johnson, 1997; Johnson, 2000; Xie et al., 2001), and therefore this information will be helpful to assess the impact of exposure on safety and efficacy.

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 must be recorded at screening:

- Disease status
- Tumor histology, grade, and stage
- BRAF V600 mutational status per local assessment
- LDH levels
- Tumor PD-L1 expression status per local assessment (current and/or historical) if available

Additionally, if known, locally assessed cancer-associated mutations (eg, NRAS), TMB and MSI status, gene signatures, and immune therapy prognostic targets should also be recorded.

8.1.3 Medical History

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

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

8.1.4 COVID-19 and/or Influenza Infections

History of COVID-19 and/or influenza infections, including dates of onset and resolution and registration on any related on-going AEs, within 6 months prior to Cycle 1 Day 1 should be recorded if known/ applicable.

8.2 Efficacy Assessments

8.2.1 RECIST Assessment of Disease Response and Progressive Disease

Tumor response will be assessed by the investigator per RECIST v1.1 criteria (Eisenhauer et al., 2009). The imaging assessment collection plan is presented in Table 11.

Imaging data will be centrally collected and checked for quality by an imaging CRO designated by the sponsor. The local investigator's assessment will be used for the primary endpoint assessment and for treatment decision making. Blinded, independent central review of the imaging data may be performed if deemed necessary (eg, by ongoing radiographic audit[s]). Images may also be used for additional exploratory research, see Section 8.7.

Refer to the imaging manual for additional information.

Table 11: Imaging Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen, and pelvis CT (with IV contrast enhancement) (**or MRI** with appropriate contrast if CT is contraindicated)[a]	**Mandated**	Mandated, see Schedule of Activities (Section 1.3)
Brain MRI (with contrast if appropriate)[b]	**Mandated**	If lesions were documented at baseline, follow same schedule (or sooner if clinically indicated) as CT/MRI of chest, abdomen, and pelvis.
CT or MRI of other metastatic sites (eg, neck)	If clinically indicated.	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis.

Abbreviations: CT=computed tomography; FDG=fluorodeoxyglucose; IV=intravenous(ly); MRI=magnetic resonance imaging; PET=positron emission tomography; RECIST=Response Evaluation Criteria in Solid Tumors.

[a] PET alone will not be considered for the disease assessment. Complementary CT and/or MRI must be performed in such cases. If a site can document that the CT performed as part of a FDG PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the FDG-PET/CT can be used for RECIST v1.1 measurements.

[b] If MRI is not available for brain imaging, CT can be accepted only after discussion with the sponsor's medical monitor.

Additional assessments should be performed if there is a suspicion of new site(s) of metastasis or of disease progression based upon clinical symptoms. The presence of a new lesion(s) should be documented on an imaging trial. All potential sites of metastases should be evaluated at each time point rather than following only sites of disease identified at baseline.

For subjects who continue trial treatment beyond initial RECIST-defined disease progression, efficacy assessment must continue.

For subjects who discontinue trial treatment without RECIST-defined disease progression as assessed by the investigator, on-trial imaging must continue until RECIST-defined disease progression, withdrawal of consent, death, or loss to follow-up, whichever occurs first.

8.2.1.1 Baseline Imaging Assessments

Imaging assessments as described in Table 11 will be performed at screening/baseline within 28 days of administration of the first dose of trial treatment (Day -28 to Day -1 prior to Cycle 1 Day 1). All sites of metastatic disease are to be reported as target or nontarget lesions at baseline and followed throughout the trial.

Any imaging assessments already completed during the regular evaluation of the subject within 28 days prior to start of treatment, including before signing the main trial ICF, can be considered as the baseline images for this trial only if they fulfill the technical imaging requirements for the trial. Any imaging assessments obtained after randomization cannot be considered baseline images. See Section 10.7.3 for details on the preferred imaging modality in Germany.

MRI is the strongly preferred modality for imaging the brain. Contrast-enhanced brain MRI is preferred; however, if MRI contrast is contraindicated, then MRI without contrast or CT with/without contrast is acceptable. If MRI is not available for brain imaging, CT can be accepted only with written approval by the sponsor's medical monitor.

NOTE:

- As a rule, target lesions must not be biopsied in this trial. Under exceptional circumstances, a biopsy may be taken on a target lesion, only after discussion with the sponsor medical director. Such exceptions are particularly relevant for single target lesions. If a biopsy at screening is allowed, the lesion must be imaged before being biopsied.
- Chest X-rays and ultrasound must not be used to measure tumor lesions.
- Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a nonmeasurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

8.2.1.2 Post-Baseline Imaging Assessments

Imaging assessments as described in Table 11 should be performed using the same imaging modality used at baseline, irrespective of trial treatment interruption or actual dosing. On-trial imaging (as described in Table 1) will be performed every 6 weeks (±7 days) for 48 weeks, and then every 12 weeks (±7 days) thereafter until documented radiographic disease progression (as assessed by the investigator; unless the investigator elects to continue treatment beyond progression), start of subsequent anticancer therapy, withdrawal of consent, death, or loss to follow-up, whichever occurs first. Imaging assessments should be scheduled using the date of first dose of trial treatment as the reference date (not the date of the previous tumor assessment) and should be respected regardless of whether treatment with trial drug is temporarily withheld or unscheduled assessments are performed. All scheduled tumor imaging, including screening, must include complete imaging of the chest, abdomen, pelvis, and brain (if applicable).

Each lesion that is assessed at baseline must be assessed by the imaging method and when possible, the same local radiologist/physician throughout the trial so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Additional imaging assessments may be performed at any time during the trial at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of 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.

If clinically stable, subjects who experience disease progression may elect to interrupt treatment by deferring the decision to continue/discontinue treatment in the trial until confirmation of disease progression approximately 6 weeks from the date of imaging demonstrating disease progression. Subjects for whom disease progression is not confirmed on subsequent imaging may resume trial treatment.

Combined PET-CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the investigators, FDG-PET scans may be performed to document progressive disease as per RECIST v1.1.

8.3 Safety Assessments

Any clinically relevant untoward events occurring during the trial must be documented as AEs. Any clinically significant abnormalities persisting at the end of the trial/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached (see Section 8.4.6).

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

8.3.1 Physical Examination

A complete (full) physical exam (according to SOC) should be performed during the screening period and at the time points specified in the Schedule of Activities (Section 1.3). At subsequent visits, the investigator or qualified designee will perform a symptom directed/clinically-indicated, brief physical examination (ie, specifically on the body part[s] or system[s] indicated by the subject's symptoms, medical history, AEs, or other findings as determined by the investigator) prior to trial treatment administration. After the first dose of trial treatment, new or worsening findings since the last assessment should be documented as AEs.

Clinically- indicated examinations may be required depending upon the individual subject and all relevant findings should be documented.

8.3.2 Body Measurements

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

8.3.3 Vital Signs

Vital signs include temperature (°C or °F), heart rate (beats/min), blood pressure (mm Hg), respiratory rate (breaths per minute), and oxygen saturation (%). Vital signs will be measured as indicated in the Schedule of Activities (Section 1.3).

The subjects should be resting for at least 10 minutes before vital signs are measured.

Temperature location (oral, axillary, rectal, or ear) selected for a subject should be measured the same throughout the trial. The temperature should be documented as a value corrected according to local standards.

8.3.4 Electrocardiograms

The ECGs will be recorded at the sites by using the standard 12-leads as indicated in the Schedule of Activities (Section 1.3), ie, at baseline and as clinically indicated.

ECGs including PR, QRS, QT, or QTcF intervals will be obtained for each subject at screening and as clinically indicated during the trial and reported in EDC. For the ECG recordings, the subject must be resting and in a supine or reclined position for at least 10 minutes. Any irregularity observed or occurring during the ECGs (eg, vomiting, cough) should either induce a repeat of the ECG or be annotated with the description and time of the occurrence.

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

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

An overall interpretation of the ECGs will be performed and reported in EDC by the investigator, or the investigator may delegate this task to a cardiologist, if applicable. The investigator should interpret ECG and sign it either digitally or manually.

8.3.5 ECOG Performance Status

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

8.3.6 Clinical Laboratory Assessments

Samples will be collected as indicated in the Schedule of Activities (Section 1.3). The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the trial. Laboratory abnormalities that are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy, or require changes in trial treatment should be documented as an AE (see Section 10.2 for additional information on reporting of laboratory abnormalities that are considered AEs). Laboratory abnormalities judged by the investigator to be associated with the underlying disease and not more severe than expected for the subject's condition, are not considered clinically significant.

When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported AE, it is not necessary to separately record the laboratory/test result as an additional event.

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

The tests detailed in Table 12 will be performed locally, as indicated. The laboratory reports must be filed with the source documents.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5. In this trial, the local laboratory values in Table 12 can be used for the evaluation of subject eligibility.

In the event that the subject undergoes local laboratory testing at a facility other than the investigative site (eg, due to hospitalization at another institution for treatment of an AE), local results should be obtained, where possible. The laboratory reports must be filed with the source documents.

Local laboratory samples must be obtained within 3 days of trial drug administration and reviewed by the investigator prior to each trial drug administration to ensure the subject can be dosed according to the dosing instructions defined in the protocol. A third-party vendor may be used to enter local lab results into the clinical database. This will be done by providing the vendor with anonymized copies of the local lab results, if allowed by local regulations. In countries where this process is not permitted, a centrally provided anonymized requisition will be used to transfer the local lab values to the third-party vendor.

Table 12: Protocol-Required Safety Local Laboratory Assessments

Hematology	**Biochemistry**		**Urinalysis**
hematocrit hemoglobin platelet count RBC count RBC indices: • MCH • MCHC • MCV • % reticulocytes WBC count with differential: • basophils • eosinophils • lymphocytes • monocytes • neutrophils	ALT albumin alkaline phosphatase amylase AST BUN calcium chloride C-reactive protein creatinine (and estimated CrCl/GFR MDRD)[a] ferritin GGT	glucose HbA1c LDH lipase magnesium phosphate potassium sodium total and direct bilirubin total protein urea uric acid	glucose leukocytes protein **Coagulation** aPTT INR PT **Pregnancy tests[b]** serum β-hCG urine pregnancy test
	Virus testing	**Endocrine/Thyroid function**	**Other**
	HBV (HBsAg, HBV DNA and anti-HBc) HCV (anti-HCV and if positive, continue with HCV RNA) HIV[c] (antigen and antibody) CMV serology and CMV DNA	Total T3[d] TSH Free T4	

Abbreviations: ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; β hCG=beta-human chorionic gonadotropin; BUN=blood urea nitrogen; CrCl=creatinine clearance; GFR=glomerular filtration rate; GGT=gamma-glutamyltransferase; HbA1C=glycosylated hemoglobin; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; 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 MDRD, [GFR in mL/min per 1.73 m^2 = 175 x SerumCr-1.154 x age-0.203 x 1.212 (if subject is black) x 0.742 (if female)]

[b] A serum pregnancy test should be performed during the screening period (within 7 days of C1D1). Additionally, a urine or serum test should be performed within 24 hours of dosing at the start of each subsequent cycle. If a urine pregnancy test is positive, a serum pregnancy test is required to confirm.

[c] HIV testing only performed if required by local regulations.

[d] Free T3 is acceptable if considered local standard.

8.4 Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established SOPs in conformity

with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

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

8.4.1 Definition of Adverse Events and Serious Adverse Events

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

8.4.2 Adverse Event Reporting

The safety reporting periods are defined in Table 13. The safety reporting period starts once the subject has signed the ICF and ends when the subject completes the last safety follow-up visit, withdraws consent, starts new anticancer treatment, or dies, whichever comes first.

Table 13: Reporting Period and Requirements

Safety Reporting Period	Reporting Requirements
Signing of ICF until first dose of trial treatment	AEs, if assessed by the investigator to be related to a protocol-mandated procedure (eg, tumor biopsy, CT scan), including washout or discontinuation of prior medications.
First dose through the last safety follow (SFU2)] visit	All AEs (see definitions in Section 10.2), regardless of causality, will be documented.
After the last safety follow-up visit through end of trial/after end of trial	There is no requirement to monitor subjects for SAEs following the protocol-required safety reporting period or after end of trial. However, if the investigator becomes aware of an SAE, it must be reported if judged by the investigator as related to trial treatment.
Refer to Section 10.2.2 for additional guidance for recording and reporting AEs and Section 7.1.2.2 for timing of safety follow-up visit(s).	

Abbreviations: AE=adverse event(s); CT=computed tomography; ICF=informed consent form; SAE=serious adverse event(s); SFU=safety follow-up.
NOTE: Any second primary malignancy(ies) regardless of relatedness to trial treatment, should be reported as an SAE at any time during or after the trial if the investigator becomes aware of such an event (see Section 8.4.3.1.2).

For details regarding follow up of AEs and SAEs, see Section 8.4.6. Refer to Section 6.2 for guidance regarding product complaints.

8.4.3 Events Requiring Immediate Reporting

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

8.4.3.1 Serious Adverse Events

8.4.3.1.1 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 principal investigator's or any investigator personnel's awareness, including receipt of relevant test results.

Updated information regarding previously reported SAEs must be submitted as it becomes available.

8.4.3.1.2 Second Primary Malignancy

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

8.4.3.2 Special Reporting Situations

8.4.3.2.1 Overdose

All cases of overdose (as defined in Section 6.7.2), whether associated with an AE or not, must be reported to the sponsor within 24 hours of knowledge of the event (see additional details in Section 6.7.2).

8.4.3.2.2 Medication Errors

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

8.4.3.2.3 Pregnancy

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

All reports of pregnancy, occurring during the trial or 4 months after the last dose of trial drug, in female subjects must be reported to the sponsor within 24 hours of knowledge of the event.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. The child must be followed at least to the age of 1 month. Pregnancy complications and elective terminations must be reported as an AE. Spontaneous abortions will always be considered an SAE.

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

8.4.4.1 Reporting Requirements for Suspected Unexpected Serious Adverse Reactions

The sponsor has a legal responsibility to notify, as appropriate and according to local regulations, both the local health 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 8.4.3.1.1).

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 health authorities and/or to the IEC/IRB according to the applicable local regulatory requirements. Relevant follow-up information of SUSARs will be communicated subsequently within the required reporting timelines. The sponsor will submit SUSARs aggregated in line listings in periods as warranted by any local health authority.

The sponsor will also communicate relevant information on SUSARs with the investigators in predefined periods and according to local regulations.

The investigator must be aware of reporting regulations/requirements for their local IEC/IRB. The clinical 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 and agreement with the investigators. SUSARs aggregated in line listings will be distributed in periods as warranted by the IEC/IRB. The investigator must review such safety information in a timely manner and signoff for the review as instructed by the sponsor, to document the awareness about the latest safety updates that may impact on the investigator's responsibilities for subject care.

8.4.4.2 Regulatory Reporting Requirements for AMPs

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

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

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

- Events that are clearly consistent with the expected pattern of the underlying disease or its progression should not be recorded as AEs or SAEs.
  - That is, the terms "Disease Progression," "Progression of Disease," or "Malignant Disease Progression" and other similar terms should not be used to describe an AE or SAE. These data are captured as efficacy assessment data only.
    - In most cases, the expected pattern of progression will be based on the response criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria.
    - Clinical symptoms may be reported as AEs or SAEs if the symptom cannot be determined as reasonably due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under trial.
- Hospitalization due solely to progression of the underlying cancer should not be reported as an SAE. See Section 10.2.1.2, under the definition of SAE, for additional reasons when hospitalizations should not be reported as SAEs.
- Unrelated Procedures: Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, a medical

condition for which an unscheduled procedure was performed should be reported if it meets the definition of an AE (eg, an acute appendicitis should be reported as the AE and not the appendectomy).

8.4.6 Follow up of Adverse Events and Serious Adverse Events

All AEs must be followed until they are resolved or until the last safety follow-up visit 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.

8.4.7 Precautions and Warnings

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

For approved products used in combination with acasunlimab, refer to the current prescribing information (eg, USPI, SmPC) for additional safety information.

8.5 Pharmacokinetics

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

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

Samples collected for predose PK 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 or samples are below limit of quantification.

Samples collected for analyses of acasunlimab plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period. Additional samples may be collected during the trial if warranted and agreed upon between investigator and sponsor, eg, for safety monitoring.

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

8.6 Pharmacodynamics

Refer to Section 8.7.2.

8.7 Biomarkers

Tumoral and peripheral samples for biomarker analyses will be collected in this trial to investigate potential predictors of efficacy or resistance to therapy, surrogate markers of clinical activity, as well as pharmacodynamic markers to confirm the biological activity of

acasunlimab ± pembrolizumab. All biomarker assessments will be conducted retrospectively at a central laboratory and specialty laboratories.

Exploratory biomarker assessments in tumor tissues and whole blood samples will focus on:

- Evaluating tumoral PD-L1 expression as a potential predictive biomarker.
- Evaluating cytokines/soluble factors at baseline and on treatment to inform mechanisms of potential immune-related safety events, as well as mechanisms of response/resistance to therapy.
- Evaluating on-treatment changes in cell-free ctDNA as a surrogate of clinical response and durability (OS/PFS/ORR/DOR).
- Evaluating the peripheral immunophenotype at baseline and on treatment as a potential predictor of response/resistance.
- Additional biomarker assessments may be performed on tumor tissues (eg, DNA or RNA sequencing, digital and histopathology) to characterize target expression, tumor microenvironment, and immune contexture to expand on the understanding of the MoA of acasunlimab as monotherapy and in combination with pembrolizumab and explore potential predictors of response/resistance to therapy.
- CCI [redacted]

Biomarker Sample Collection

Samples for biomarker analyses will be collected as specified in the Schedule of Activities (Section 1.3). Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the trial, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the trial is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

CCI [redacted] will be based on subject imaging data collected as part of the RECIST tumor assessment (see Section 8.2.1).

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 Biomarker Assessments in Tumor Samples

Subjects must provide an FFPE tumor tissue sample that is obtained before administration of trial treatment and originates from the advanced and/or metastatic setting (ie, Stage IIIB, IIIC, IIID, or IV). Fresh tumor biopsy (defined as ≤ 3 months old) is preferred; archival tumor tissue is acceptable. If a fresh tumor sample is provided, it needs to be collected after progression on or discontinuation of last prior treatment and prior to Cycle 1 Day 1.

If deemed necessary by the investigator, the subject may be called in for an unscheduled visit, and additional tumor tissue samples may be collected if subjects have unscheduled biopsies or tumor tissue resection during the course of the trial. If clinically feasible, tumor biopsies should be performed at disease progression, preferably from a newly diagnosed lesion, if any.

NOTE: All tumor tissue samples must be FFPE and of sufficient histological quality. The tumor sample can be from a core biopsy (preferably not smaller than 18-gauge needle), or from resected tumor tissue. Fine needle aspirates, cell blocks, cell pellets, clots, bone and bone marrow-derived biopsies, and cytological specimens are not acceptable. FFPE tissue blocks are preferred; if FFPE slides are provided, slides need to be freshly cut. Refer to the laboratory manual on prespecified maximum allowed cut-date and preparation.

Biomarker analyses in tumor samples collected at baseline and/or upon disease progression may enable the identification of potential biomarkers predictive of response or resistance to trial treatment. Tumor tissues may be evaluated for target expression (protein or RNA), as well as undergo molecular profiling to identify potential mechanisms of disease response or resistance to therapy.

8.7.1.1 Protein Expression Analyses

Expression of proteins related to melanoma biology or acasunlimab's mode of action may be evaluated in tumor biopsies by IHC on an automated staining platform. Tumor sections will be scored by a certified pathologist, and digital images will be made from stained tumor sections to be used for exploratory digital pathology analyses.

8.7.1.2 RNA Expression Analyses

RNA sequencing may be performed on tumor biopsies to determine PD-1, PD-L1, and 4-1BB mRNA expression levels, as well as to evaluate other potential gene expression signatures associated with response or resistance to PD-1/PD-L1 targeting therapies, acasunlimab's MoA and target biology, or cancer biology in general.

8.7.1.3 DNA Analyses

Tumor biopsies may also be analyzed using NGS for analyses of DNA mutations, copy number variations, TMB, microsatellite instability, indels, and/or rearrangements or polymorphisms in genes associated with resistance to PD-1/PD-L1 targeting therapies acasunlimab's proposed mode of action, or cancer biology.

If DNA/RNA research evaluations are performed, the results may be reported in a separate report. Where required by local or county specific regulations, each subject must sign a separate ICF indicating agreement to provide samples for genomic biomarker analysis (DNA and RNA).

8.7.2 Biomarker Assessments in Blood Samples

Biomarker assessments may also be performed using whole blood samples to investigate potential pharmacodynamic markers and explore the relationship to the efficacy and/or mode of action of acasunlimab with or without pembrolizumab. Assessments will be performed at baseline (before infusion at Cycle 1 Day 1) and at later time points/cycles during treatment in order to enable correlation analyses with response to treatment or disease biology.

8.7.2.1 Immunophenotyping Analyses

Immunophenotyping may be performed on PBMCs at baseline and during treatment at planned visits so changes associated with the mode of action of acasunlimab ± pembrolizumab, subject response to trial treatment, and disease biology can be evaluated.

8.7.2.2 Cytokine (Soluble Factors) Analyses

The levels of cytokines/chemokines/soluble factors at baseline and during treatment at planned visits will be analyzed to inform mechanisms of potential immune-related safety events as well as potential mechanisms of response/resistance to treatment with acasunlimab as monotherapy and in combination with pembrolizumab.

8.7.2.3 Proteomics

The levels of soluble proteins (eg, soluble 4-1BB, granzyme B) in blood samples may be determined at baseline and during treatment at planned visits so changes associated with the mode of action of acasunlimab ± pembrolizumab, subject response to trial treatment, and/or disease biology can be evaluated.

8.7.2.4 Cell-Free DNA and Tumor-Derived DNA Analyses

Circulating cfDNA, including ctDNA, may be measured, and analyses such as DNA mutations, copy number variations, microsatellite instability, TMB, indels, and/or rearrangements in genes may be performed to evaluate the association of such biomarkers with the mode of action of acasunlimab as monotherapy and in combination with pembrolizumab, subject response to trial treatment, or disease biology.

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 1.3).

Serum samples will be screened for ADAs binding to acasunlimab and the titer of confirmed positive samples will be reported. Plasma concentrations of acasunlimab will be analyzed (see Section 8.5) and those data will be used to for interpretation of the ADA data. The ADA samples may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the trial period for further characterization of immunogenicity.

Predose samples for soluble target analyses 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 or samples are below limit of quantification.

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

Further details are included in the laboratory manual.

8.9 Clinical Outcome Assessments/Patient-Reported Outcomes

The effect of the treatments and the cancer on various aspects of the subject's health-related quality of life will be assessed by the questionnaires described below.

All COAs/ePROs will be completed at the time points indicated in the Schedule of Activities (Section 1.3), using an electronic solution (eg, tablet) collected via a central vendor.

Subject questionnaires should be completed in the language most familiar to the subject. The subject should be given the questionnaire(s) to be completed at the scheduled visit before any clinical assessments are conducted (unless hospital care cannot be delayed to accommodate completion of the questionnaire) and before receiving any trial treatment. The subject should be given sufficient space, time, and privacy to independently complete the questionnaire.

Subject's refusal or inability (eg, due to medical reasons) to complete all or any part of a questionnaire should be documented and should not be captured as a protocol deviation, but the lack of completion should be documented with the precise reason. FACT-GP5 will be administered first followed by FACT-M as indicated in the Schedule of Activities (Section 1.3).

8.9.1 FACT-GP5

The GP-5 is a single-item measure that evaluates a subject's overall distress related to cancer (Griffiths et al., 2022). Subjects respond to the question, "I am bothered by side effects of treatment," on a 5-point Likert scale (0 = Not at all; 4 = Very much). This question provides an overall measure of the burden of disease and treatment, capturing a snapshot of the subject's well-being.

8.9.2 FACT-M

The FACT-M is a validated, self-reported questionnaire designed to assess quality of life in subjects with melanoma (Cormier et al., 2008). It consists of multiple subscales, which measure physical, social, emotional, and functional well-being, as well as melanoma-specific concerns. The questionnaire includes approximately 51 items, with each item rated on a 5-point Likert scale (0 = Not at all; 4 = Very much). Higher scores indicate better quality of life. The FACT-M is divided into 2 main sections:

- **Core FACT-G Scale**: This scale measures general quality of life across 4 subdomains: physical well-being, social/family well-being, emotional well-being, and functional well-being.
- **Melanoma-Specific Scale**: This additional scale includes items addressing issues unique to melanoma, such as concerns about skin appearance and treatment side effects. The FACT-M provides a comprehensive overview of how melanoma impacts a subject's quality of life and can be used to track changes over time or in response to treatment.

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.

9.1 Statistical Hypotheses

The trial is not designed to detect statistically significant differences between arms.

9.2 Population for Analyses

Analysis Set	Definition
Full Analysis Set (FAS)	FAS comprises all randomized subjects with available baseline tumor assessment that received at least 1 dose of trial treatment. FAS is used for efficacy analyses.
Safety Analysis Set (SAS)	SAS comprises all randomized subjects that received at least 1 dose of trial treatment. SAS is used for safety summaries as well as summaries of demographics and baseline characteristics.
Response-evaluable set	Subjects in FAS with at least 13 weeks of follow-up from first dose to data cut off. This set is used for futility analyses of ORR
Pharmacokinetics analysis set (PKS)	PKS includes all subjects who receive at least 1 dose of trial treatment and have at least 1 post-baseline concentration measurement. PKS is used for analyses of PK parameters.
Anti-drug antibody analysis set (ADAS)	ADAS includes all subjects who receive at least 1 dose of treatment and have at least 1 post-baseline ADA measurement. ADAS is used for ADA summaries.

9.3 Statistical Analyses

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

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

9.3.1 General Considerations

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

Baseline refers to the last observation prior to first trial drug administration.

9.3.2 Primary Endpoint Analysis

ORR is defined as the proportion of subjects with a confirmed response of CR or PR according to RECIST v1.1 as assessed by the investigator. Subjects who are nonevaluable or without any available postbaseline response assessments are counted as nonresponders. A minimum of 5 weeks from baseline is required for a BOR of SD.

ORR and its exact 2-sided 95% confidence interval, using the Clopper-Pearson method, will be presented by treatment arm. The Cochrane-Mantel-Haenszel chi-square test, stratified by the randomization stratification factors, will be used to compare ORR between the 2 treatment arms, at the 1-sided 2.5% level of significance, and the odds ratio will be presented with a 2-sided 95% confidence interval.

9.3.3 Secondary Endpoint Analyses

Time to Response

TTR per RECIST v1.1 as assessed by the investigator is defined as the time from the date of first administration of trial drug to the first documented response of either CR or PR, which must be subsequently confirmed.

TTR will be summarized by arm using the Kaplan-Meier plot. The Kaplan-Meier method will also be used to estimate median TTR with 95% confidence interval by 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 anti-cancer therapy.

TTR is only defined and calculated for subjects with a confirmed response.

Duration of Response

DOR per RECIST v1.1 as assessed by the investigator is defined as the time from first documentation of objective response (PR or CR) that is subsequently confirmed, to the first documentation of disease progression or death due to any cause, whichever comes first.

DOR will be summarized by arm using the Kaplan-Meier plot. The Kaplan-Meier method will also be used to estimate median DOR with 95% confidence interval by arm. Subjects will be censored according to Table 14. DOR is only defined and calculated for subjects with a confirmed response.

Table 14: Censoring Rules for DOR and PFS

Event	Date of Censor	Applies to
No evaluable baseline tumor assessments	Date of first dose	PFS
No evaluable post-baseline tumor assessments	Date of first dose	PFS
New anticancer therapy initiated during trial	Date of last evaluable tumor assessment prior to or at start of the new anticancer therapy	DOR and PFS
Discontinuation or data cut-off without event of interest	Date of last evaluable tumor assessment	DOR and PFS
Event of interest after more than 1 missed or nonevaluable tumor assessments	Date of last evaluable tumor assessment prior to non-evaluable/missing assessments	DOR and PFS

NOTE: Censor at whichever censor date occurs first unless event of interest already occurred.

Progression-Free Survival

PFS is defined as the time from the date of first administration of trial drug to the date of the first documented progression or death due to any cause, whichever occurs first.

PFS will be summarized by arm using the Kaplan-Meier plot. The Kaplan-Meier method will also be used to estimate median PFS with 95% confidence interval by arm. Subjects will be censored according to Table 14.

Overall Survival

OS is defined as the time from date of first administration of trial drug to date of death due to any cause. OS will be summarized by arm using the Kaplan-Meier plot. The Kaplan-Meier method will also be used to estimate median OS with 95% confidence interval by arm. OS for a subject without a documented death at the time of the analysis will be censored at the last date the subject is known to be alive.

9.3.4 Exploratory Endpoint(s) Analyses

Exploratory endpoint analyses will be detailed in the SAP.

9.3.5 Safety Analyses

Adverse Events

Each AE reported by the investigator will be mapped to a MedDRA preferred term and a system organ class. Summary tables for AEs will include AEs that started or worsened during the on-treatment period (ie, TEAEs). This period is defined as the period from the first dose of IMP to 90 days after the last dose of IMP, the start of subsequent anticancer therapy, trial discontinuation, death, or data cutoff, whichever occurs first.

The incidence of TEAEs will be summarized by MedDRA system organ class and/or preferred term, severity (based on grades of CTCAE v5.0, with the exception of CRS which will be graded according to the ASTCT criteria (Lee et al., 2019)), and relationship to trial drug.

All TEAEs, including SAEs, during the on-treatment period will be summarized by treatment arm.

All deaths (on treatment and post-treatment) will be summarized by treatment arm and listed.

Kaplan-Meier plots will be presented by treatment arm for selected safety endpoints such as time to treatment discontinuation due to AE. For subjects without the AE of interest, time will be censored at the end of the on-treatment period.

Further summaries of AEs will be specified in the SAP.

Clinical Laboratory Data

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

Each laboratory parameter will be summarized by treatment arm, visit, and grade. The worst postbaseline on-treatment CTCAE grade (regardless of the baseline status) will also be

summarized across scheduled and unscheduled visits. Each subject will be counted only once for the worst grade observed postbaseline.

Further summaries of laboratory values may be specified in the SAP.

Other Safety Data

Overall interpretation by investigator will be summarized by cycle and arm. Data on vital signs will be summarized by arm.

9.4 Planned Analyses

9.4.1 Interim Analysis

An interim analysis for futility will be conducted after approximately 20 subjects per arm are evaluable for ORR. Futility will be based on totality of data, with emphasis on ORR.

Using the PPoS framework (Lee and Liu, 2008), assuming 20 subjects at the interim analysis, 15 responders out of 45 subjects at the final analysis, a 20% ORR benchmark, a mildly informative Beta(0.2,0.8) distribution for PPoS, the probabilities of success are 4.4% and 14.9% for 4 and 5 responders out of 20 subjects, respectively. This means that futility for ORR will be considered if 4 or less subjects out of 20 evaluable subjects are responders.

9.4.2 Primary Analysis

The primary analysis will be conducted approximately 12 months after the last subject's first dose. At this time, a data sweep will be performed to determine the survival status of previously discontinued subjects.

9.4.3 Final Analysis

A final analysis will be conducted when all subjects have completed the trial (including all post-treatment follow-up). At this time, a final data sweep will be performed to determine the survival status of previously discontinued subjects.

9.5 Sample Size Determination

The treatment will be considered promising if the exact 1-sided 95% lower confidence limit for ORR exceeds 20% percent. With 45 subjects per arm and a true ORR of 35% and 40%, the power to meet this criterion is 65% and 86%, respectively. To reject the null hypothesis (ORR = 20%), at least 15 responders out of 45 subjects are required.

10 APPENDICES: SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and Ethical Considerations

The principles of the Declaration of Helsinki, the consolidated ICH-GCP, and applicable regulations and national law(s) (eg, 21 CFR and European regulation 536/2014 for clinical studies, 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 studies 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 IEC/IRB by the investigator and reviewed and approved by the IEC/IRB before the trial is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial subjects. In these emergency situations, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s), will be submitted to the IEC/IRB and, if required, health authorities for approval as soon as possible.

10.1.2 Investigator Responsibilities

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

NOTE: a ‘serious breach’ means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

10.1.3 Independent Ethics Committee or Institutional Review Board

This trial will be undertaken only after the IEC/IRB has given written approval of the final protocol, amendments to the protocol (if applicable), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this written approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data, or trial conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and written approval before implementation of the change(s).

The IB and updates to the IB, unexpected SAEs where a causal relationship cannot be ruled out, serious breaches, serious noncompliance, annual written summaries of the trial status, and deviations to the protocol implemented to eliminate immediate hazards to the subjects must be submitted to the IEC/IRB.

Interim reports on the trial and/or review(s) of trial progress will be submitted by the investigator, where applicable, to the IEC/IRB at intervals stipulated in its guidelines.

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

10.1.4 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health 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 IEC/IRB and health authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to subjects (see Section 10.1.1) or changes that involve logistical or administrative aspects only (eg, change in the sponsor's medical director 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 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 health 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 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 site monitor 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. The subject screening log will be filed in the Investigator Site file and the Trial Master File.

10.1.6 Informed Consent Process

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

It is the personal responsibility of the investigator or an authorized member of the trial-site personnel to explain to potential subjects (or their legally acceptable representatives) 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 and without penalty or loss of benefits to which subjects is otherwise entitled. 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 log for the purposes of long-term follow up if needed and that their records may be accessed by IEC/IRB and health authorities, and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations.

By signing the ICF the subject (or legally acceptable representative) 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 (or his/her legally acceptable representatives) will be given sufficient time to read the ICF and the opportunity to enquire about details of the trial prior to deciding whether to participate in the trial. After this explanation and before any trial-specific procedure is performed, consent should be appropriately documented by means of either the subject’s or their legally acceptable representative’s personally dated signature.

Subjects (or his/her legally acceptable representative) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, European regulation 536/2014

for clinical studies, local regulations, ICH guidelines, HIPAA, and EU GDPR requirements, where applicable, and the IEC/IRB or trial center. The investigator or authorized person obtaining the informed consent must also sign and date the ICF. After having obtained the consent, a copy of the ICF must be given to the subject.

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

The sponsor will, on an ongoing basis, assess whether reconsent of subjects is needed and revise the ICF whenever any important new information becomes available that may be relevant to the subject's consent.

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, or the rescreening occurs > 28 days from the previous ICF signature date.

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

10.1.7 Data Protection

The investigator will ensure that the confidentiality of all subjects’ data will be preserved. In the eCRF or any other documents submitted to the sponsor/sponsor’s representative, the subjects will not be identified by their names, but by an identification code, which consists of an assigned number in the trial. The confidential subject identification code and the signed ICF will be maintained by the investigator in strict confidence.

In relation to the collection and handling of data, including any personal data, potential risks to the subjects have been assessed and adequate technical and organizational measures are implemented to ensure a level of security appropriate to the risk.

The security measures implemented entail among other things that:

- Access to data has been restricted so that access is only granted to authorized individuals.
- Data are only stored on IT systems and networks that are protected against virus, malware, and unauthorized access.
- Data are backed-up at regular intervals. In case of a data breach, a clear allocation of roles and responsibilities for managing the data breach, including notifying affected subjects and authorities, has been established in order to mitigate any adverse impact on the subjects.

Additional technical security measures implemented include that:

- All data are encrypted when at rest.
- Data have been pseudonymized to the effect that only authorized individuals can link data to identified individuals.
- A data breach response plan has been established.

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

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place, as detailed above. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or their legally acceptable representative) 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

Safety Committee

The sponsor Safety Committee is a cross-functional body dedicated to safeguarding subject welfare by continuously evaluating the evolving benefit-risk profile of acasunlimab and implementing timely risk management strategies. The committee analyzes emerging safety data, collaborates with the Pharmacovigilance Board which holds the authority to approve all emerging safety decisions that may impact clinical development, trial programs, to address safety concerns, and determines the safety of continued development, recommending necessary actions to protect subjects. The committee is empowered to temporarily pause or stop enrollment if treatment-emergent toxicity results in an unfavorable change to the benefit-risk profile and ensures thorough data evaluation before proceeding with enrollment.

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 health authorities, as required.

Other Committees

This trial will be commissioned by a Steering Committee. Further information can be found in the Steering Committee Charter.

10.1.9 Dissemination of Clinical Trial Data

10.1.9.1 Central Laboratory Data

While all central laboratory data will be shared with the investigator, the following laboratory results will not be made immediately available to the investigator: PK, ADA, and exploratory biomarkers. As they are not necessary for the treatment of subjects, these results may be made available as part of the CSR or as otherwise specified in the laboratory manual.

10.1.9.2 Protocol Registration and Trial Results

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 4.4.3) 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).

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

10.1.10.1 Data Quality Management

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

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

10.1.10.2 Record Retention

In compliance with ICH GCP E6(R2), the investigator/institution will maintain all eCRFs and all source documents, as well as a source document location list, that support the data collected from each subject, as well as all trial documents as specified in ICH GCP Guideline Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as

specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained for 25 years after end of trial. These documents will be retained for a longer period if required by the applicable regulatory requirements. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Medical records (subjects' hospital records) are 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 health 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 or delegate will use a combination of remote and on-site monitoring to monitor this trial according to the strategy defined in the monitoring plan(s). The sponsor or delegate will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a trial-site visit log that will be kept at the trial site. The first post-initiation visit will be made as soon as possible after enrollment (ie, the first subject has signed the ICF) has begun. At these visits, the monitor will verify the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and trial-site personnel and are accessible for verification by the sponsor site monitor. 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.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. The author of an entry in the source should be identifiable.

Source documents may also include data captured in the IRT system (if used, such as the unique subject identifier and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). For this trial, the CRF entry may be considered as source for the following: demographic data (race, ethnicity, gender and sex assigned at birth. Additionally, source data may be recorded directly electronically (eg, ECGs, COAs). Such data are considered source data and are accessible by both the investigator and sponsor. Specific details required as source data for the trial will be reviewed with the investigator before the trial, described in the monitoring guidelines (or equivalent), and captured in a source data verification log at site.

For each subject, the investigator must indicate in the hospital/medical source records that the subject participates in this trial and the date of obtaining the ICF. The records should document data on the condition of the subject at the time the subject is enrolled in the trial, to enable verification of eligibility. Limited redacted source documents may be shared with the sponsor during screening for eligibility, where permitted by local regulations. This allows the sponsor's medical monitor to have sufficient information to provide guidance, answer questions, and support investigators regarding the eligibility of their patients. Signed and dated ICFs will be stored in the investigator site file and archived according to local requirements.

In addition, the following information, at the minimum, will also be recorded in the hospital/medical source records for each subject:

- subject's name and date of birth
- screening/subject/randomization number
- trial identification
- confirmation of eligibility for participation in the trial, including diagnosis
- medical history
- date of each visit
- any assessment performed eg, results of safety and efficacy evaluations
- concomitant medications
- occurrence of any AEs/SAEs (including description and duration)
- status of the subject at the end of trial
- reason for treatment discontinuation/trial withdrawal, if applicable

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 (corrections must be verified and approved by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form.):

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

10.1.12 Trial and Site Start and Closure

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

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 acasunlimab development.

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

If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the health authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject(s) and should ensure appropriate subject therapy and/or follow up.

10.1.13 Publication Policy

All information, including but not limited to information regarding acasunlimab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including exploratory research data, generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this trial and will not use it for other purposes without the sponsor's prior written consent. CROs involved in the trial are not permitted to publish without the sponsor's prior written approval.

The investigator understands that the information developed in the trial will be used by the sponsor in connection with the continued development of acasunlimab, and thus may be shared as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical trial to be used, the investigator is obligated to provide the sponsor with all data obtained in the trial.

Trial subject identifiers will not be used in publication of results. Any work created in connection with performance of the trial and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines (Battisti et al., 2015; ICMJE, 2010; ICMJE, 2023) the sponsor in conjunction with any collaborative group(s), shall have the right to publish such primary

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

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

10.2.1 Definitions

10.2.1.1 Definition of Adverse Event

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

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

10.2.1.2 Definition of Serious Adverse Event

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

- Is fatal or life-threatening
  - The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  - Hospitalizations for the following reasons should not be reported as SAEs:
    - Routine treatment or monitoring of the underlying disease, not associated with any deterioration in the condition
    - Solely due to progression of the underlying cancer
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the underlying disease and has not worsened since signing the ICF
    - Social reasons and respite care in the absence of any deterioration in the subject’s general condition
    - Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above
- Is medically significant, as assessed by the investigator/sponsor based on medical judgement.ie, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above

10.2.2 Procedures for Recording and Reporting

10.2.2.1 Recording

All AEs, serious or nonserious, must be documented as outlined in Table 13.

- The diagnosis/cause of an AE should be documented rather than the symptoms of the AE.
- If no diagnosis is available, then each sign and symptom should be documented as an individual AE.
- All AEs that occur during the AE reporting period must be documented, whether or not the event is considered treatment-related.
- All AEs should be documented and reassessment made at each visit (or more frequently, if necessary).
- Final assessment of AEs must be performed by a medically qualified person.

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

- Whenever possible, a diagnosis should be provided (eg, anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation for the abnormality is found.
- NOTE: A CTCAE Grade 3 or 4 laboratory abnormality does not automatically indicate an SAE.

10.2.2.2 Reporting

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

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

10.2.3 Evaluation of Adverse Events

10.2.3.1 Severity

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

CRS,ICANS, and HLH will be evaluated according to the ASTCT criteria (Hines et al., 2023; Lee et al., 2019) (Sections 10.9 to 10.13). CTLS will be evaluated according to the Cairo-Bishop classification (Coiffier et al., 2008) (Section 10.8).

10.2.3.2 Relationship to Trial Treatment

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

The investigator must assess whether or not the event is related to the individual trial treatment(s) (inclusive of all IMPs and AMPs). The relationship is to be judged using the following terms:

- Related
- Not related

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

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

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 receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 4 months after the last dose of trial treatment. Please refer to Table 15 for guidance on contraception required during and after specific GCT1046-07 trial treatment.

If relevant (based on treatment regimen) and allowed by local regulations, if female subjects of reproductive potential plan to become pregnant after the trial ends, consider discussing option for cryopreservation prior to dosing.

10.3.1 Definition of Reproductive Potential

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

- A postmenopausal state is defined as no menses in subjects >45 years of age for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in subjects not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

10.3.2 Contraception Methods for Female Subjects

Adequate contraception is defined as highly effective methods of contraception (see Table 15). Birth control methods are considered highly effective if they have a failure rate of less than 1% per year when used consistently and correctly.

Hormonal contraception may be susceptible to interaction with trial treatment, which may reduce the efficacy of the contraception method, and therefore must be supplemented with a barrier method for non-vasectomized male partner (preferably a condom with spermicidal foam/gel/film/cream/suppository). The chosen contraception method must not be contraindicative, eg, estrogen containing hormonal contraception in subjects with previous thrombotic events.

All female subjects must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction during the trial and for 4 months after receiving the last dose of trial treatment.

Table 15: Highly Effective Methods of Contraception

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

Adapted from "Recommendations related to contraception and pregnancy testing in clinical studies, version 1.1." (CTFG, 2020).

[a] Contraception methods that, in the context of this guidance, are considered to have low user dependency.

[b] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the female subject of reproductive potential (ie, the trial subject) and that the vasectomized partner has received medical assessment of the surgical success.

[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the trial treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

10.4 Appendix 4: Sample Storage and Destruction

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

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

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

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

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required trial and subject number so that any remaining samples and any other components from the cells can be located and destroyed. However, information collected from samples before the request for destruction will be retained by Genmab.

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

10.5 Appendix 5: ECOG Performance Status

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

Source: (Oken et al., 1982).

10.6 Appendix 6: Definition of Response (RECIST v1.1)

RECIST v1.1 will be used to define response (Eisenhauer et al., 2009).

Table 16: Definition of Response (RECIST V1.1)

	Category	Criteria
Based on target lesions	CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
	PR	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
	SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on trial.
	PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on trial (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
Based on nontarget lesions	CR	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
	Non-CR/ Non-PD	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
	PD	Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

10.7 Appendix 7: Country-Specific Considerations

10.7.1 IMP/AMP EU Authorisation Status

Drug Name	IMP or AMP	EU Authorisation Status
Acasunlimab	IMP	Unauthorised
Pembrolizumab	IMP	Authorised
Dexamethasone, methylprednisolone, prednisone (or equivalent)	AMP	Authorised

Abbreviations: AMP=auxiliary medicinal product; EU=European Union; IMP=investigational medicinal product

10.7.2 France-Specific Requirements

Section	Country-Specific Language
5.2, Exclusion criterion #19FR	The following exclusion criteria apply in France: • Persons deprived of liberty by judicial or administrative decision. • Persons subject to forced psychiatric care. • Persons of full age who are subject to a legal protection measure (under guardianship or curatorship). • Persons under a legal protection measure. • Persons who are not affiliated with a social security or equivalent plan.

10.7.3 Germany-Specific Requirements

Section	Country-Specific Language
8.2.1.1. Baseline Imaging Assessments	In Germany, the preferred imaging modality for all radiologic assessments should be MRI, unless the investigator deems this option is contraindicated for this trial.

10.8 Appendix 8: Classification and Management of Laboratory and Clinical Tumor Lysis Syndrome

Subjects who are considered to have an increased risk for TLS, eg, due to the type of lymphoma, the tumor burden (bulky disease and/or elevated LDH), renal impairment and/or elevated uric acid should be considered for hydration and prophylactic treatment with a uric acid lowering agent as well as frequent monitoring, according to local standards or available guidelines (Coiffier et al., 2008).

In addition, close monitoring of laboratory parameters to allow for early diagnosis of possible TLS is recommended at the investigator's discretion. If signs of TLS occur, supportive therapy, including rasburicase, may be used as clinically indicated at the investigator's discretion.

In laboratory TLS, 2 or more metabolic abnormalities (ie, hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward.

CTLS requires the presence of laboratory TLS **plus** an increased creatinine level, seizures, cardiac dysrhythmia, or death.

Definitions of Laboratory and Clinical Tumor Lysis Syndrome

Metabolic Abnormality	Criteria for Classification of Laboratory TLS	Criteria for Classification of CTLS
Hyperuricemia	Uric acid >8.0 mg/dL (475.8 µmol/liter) in adults or above the upper limit of the normal range for age in children	Not Applicable
Hyperphosphatemia	Phosphorus >4.5 mg/dL (1.5 mmol/liter) in adults or >6.5 mg/dL (2.1 mmol/liter) in children	Not Applicable
Hyperkalemia	Potassium >6.0 mmol/liter or 6 mg/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dL (1.75 mmol/liter) or ionized calcium <4.5 mg/dL (1.12 mmol/liter)[a]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[b]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 ml/kg/hr for 6 hr

CTLS= clinical tumor lysis syndrome; TLS=tumor lysis syndrome.

Note: In laboratory tumor lysis syndrome, 2 or more metabolic abnormalities must be present during the same 24 hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

[a]The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8×(4 – albumin in grams per deciliter).

[b]Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome. Data about acute kidney injury are from (Levin et al., 2007).

Source: (Howard et al., 2011)

Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome and Grading

Complication	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine[a]	1.5×ULN	> 1.5-3.0×ULN	> 3.0-6.0×ULN	> 6.0×ULN	Death
Cardiac arrhythmia	Intervention not indicated	Nonurgent medical intervention needed	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	
Seizure	None	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	

ADL=activities of daily living; CHF=congestive heart failure; ULN=upper limit of normal.
[a] If no institutional ULN is specified, ULN is defined as follows: female 105.6 µmol/L, male 114.4 µmol/L.
Source: (Coiffier et al., 2008)

Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥0.5 mmol/L increase from prior value (even if potassium WNL)	Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥0.2 mmol/L increase in potassium, but still < ULN, manage as per potassium ≥ ULN. Otherwise re-check in 1 hour. Resume per protocol testing if change in potassium is <0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis syndrome. At the discretion of the investigator, consider re-checking TLS laboratory values prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be re-checked within 24 hours.
Potassium > upper limit of normal	Perform STAT ECG and commence telemetry. Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg intravenously (IV) × 1. Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias.

Abnormality	Management Recommendations
	Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis syndrome.
Potassium ≥6.0 mmol/L (6.0 mEq/L) and/or symptomatic (eg, muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	Perform STAT ECG and commence telemetry. Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg IV × 1. Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. Administer sodium bicarbonate 1 – 2 mEq/kg IV push. If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. Re-check potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥8.0 mg/dL (476 µmol/L)	Consider rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥10 mg/dL (595 µmol/L) OR Uric acid ≥8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥0.3 mg/dL (≥0.027 mmol/L) from predose level	Administer rasburicase (dose per institutional guidelines). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Notify nephrology (or other acute dialysis service). Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If uric acid <8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (eg, muscle cramps, hypotension, tetany, cardiac arrhythmias)	Administer calcium gluconate 50 – 100 mg/kg IV slowly with ECG monitoring. Telemetry. Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. Calculate corrected calcium and check ionized calcium if albumin is low.
Hyperphosphatemia	
Phosphorus ≥5.0 mg/dL (1.615 mmol/L) with ≥0.5 mg/dL	Administer a phosphate binder (eg, aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate).

Abnormality	Management Recommendations
(0.16 mmol/L) increase	Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥10 mg/dL). Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If phosphorus <5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis syndrome.
Creatinine	
Increase ≥25% from baseline	Start or increase rate of IV fluids. Re-check potassium, phosphorus, uric acid, calcium and creatinine in 1 – 2 hours STAT.

ECG=electrocardiogram; IV=intravenous; TLS=tumor lysis syndrome; ULN=upper limit of normal; WNL=within normal limits.

10.9 Appendix 9: CRS Grading and Management Guidance Based on the ASTCT Guidelines

Harmonized definitions and grading criteria for CRS, per the ASTCT, are presented below.

Grading of Cytokine Release Syndrome

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever[a]	≥38.0°C	≥38.0°C	≥38.0°C	≥38.0°C	Death due to CRS in which another cause is not the principle factor leading to this outcome
With hypotension[b]	None	Not requiring vasopressors	Requiring 1 vasopressor with or without vasopressin	Requiring ≥ 2 vasopressors (excluding vasopressin)	
And/or hypoxia[b]	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[c] (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.
[a] 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 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.
[b] 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.
[c] 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)

CRS Management Guidance Based on the ASTCT[a] Guidelines

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Glucocorticoids
Grade 1	Hold trial treatment until resolution of CRS. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly start up broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended	Consider anticytokine therapy[e] in certain cases, eg, advanced age, high tumor burden, circulating tumor cells, fever refractory to antipyretics. Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)	Dexamethasone 10-20 mg per day (or equivalent) may be initiated. Note: In case of concurrent ICANS, initiation of corticosteroids are highly recommended (see ICANS guidelines in Section 10.11).

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Glucocorticoids
	until fever and any existing neutropenia resolve. Supportive care per institutional standard of care (antipyretics and IV hydration) Closely monitor neurologic status.		
Grade 2	Hold trial treatment until resolution of CRS. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. 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	Anticytokine therapy recommended.[e] If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)	Consider dexamethasone 10-20 mg per day (or equivalent). Note: In case of concurrent ICANS, initiation of corticosteroids is highly recommended (see ICANS guidelines in Section 10.11).
Grade 3	Permanently discontinue trial treatment unless the Grade 3 CRS has improved to Grade 1 or resolved within 72 hours. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Management in intensive care unit. Vasopressor support and/or supplemental oxygen.[c] Consider cardiac echocardiogram. IV fluids as indicated.	Anticytokine therapy recommended.[e] If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and consider alternative anticytokine therapy. Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)	Dexamethasone (eg, 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day
Grade 4	Permanently discontinue trial treatment. In-person evaluation by medical professional, ideally at site or center with experience managing CRS.	Anticytokine therapy recommended.[e] If CRS is refractory to initial cytokine therapy, initiate/increase dose of corticosteroid therapy and	Dexamethasone (eg, 10-20 mg IV every 6 hours). If no response, initiate methylprednisolone 1000 mg/day

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Glucocorticoids
	Investigate for infection and rapidly start up broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Management in intensive care unit. Mechanical ventilation and/or renal replacement therapy may be required. Vasopressor support as indicated.[c] IV fluids as indicated. Consider and assess for development of macrophage activation syndrome/ hemophagocytic lymphohistiocytosis (MAS/HLH)[d], including monitoring of fibrinogen and triglyceride levels.	consider alternative anticytokine therapy. Note: In case of concurrent ICANS choose alternative to tocilizumab (eg, siltuximab, anakinra)	

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

[a] Source: (Lee et al., 2019)

[b] Refer to tocilizumab, siltuximab, or anakinra local prescribing information for product details.

[c] See high-dose vasopressors in table below.

[d] Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroid.

[e] 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.

High-Dose Vasopressors (all Doses are Required for ≥ 3 Hours)

Pressor	Dose
Norepinephrine monotherapy	≥ 20 µg/min
Dopamine monotherapy	≥ 10 µg/kg/min
Phenylephrine monotherapy	≥ 200 µg/min
Epinephrine monotherapy	≥ 10 µg/min
If on vasopressin	Vasopressin 1 norepinephrine equivalent of ≥ 10 µg/min[a]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 µg/min[a]

[a] Vasopressor equivalent equation: norepinephrine equivalent dose = [norepinephrine (µg/min)] + [dopamine (µg/kg/min) / 2] + [epinephrine (µg/min)] + [phenylephrine (µg/min) / 10]

Source: (Lee et al., 2019)

10.10 Appendix 10: Grading of HLH

Grading schema for HLH based largely on the NCI CTCAE v5.0 using the "Immune system disorder, other" category, per the American Society for Transplantation and Cellular Therapy (ASTCT) is presented below (Hines et al., 2023). For recommendations on the management of HLH, refer to Section 6.7.1.2.2.2.

HLH Grade*				
1	2	3	4	5
Asymptomatic or mild symptoms; requires observation and/or clinical and diagnostic evaluation. Intervention not indicated.	Mild to moderate symptoms, with intervention indicated (eg, immunosuppressive agents directed at HLH, transfusions for asymptomatic hypofibrinogenemia)	Severe or medically significant but not immediately life- threatening (eg, coagulopathy with bleeding requiring transfusion support, or hospitalization required for new-onset acute kidney injury, hypotension, or respiratory distress)	Life-threatening consequences: urgent intervention indicated (eg, life-threatening bleeding or hypotension, respiratory distress requiring intubation, dialysis indicated for acute kidney injury)	Death

* Not attributable to other causes; defined by the development of pathological and biochemical features of HLH that is attributable to trial treatment and associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia and hepatic transaminitis (>5 × ULN). While HLH-like manifestations are frequently seen in inpatients with severe CRS (as defined by ASTCT), HLH is often delayed in onset and manifests as CRS is resolved/resolving.
Source: (Hines et al., 2023)

10.11 Appendix 11: ASTCT ICANS Consensus Grading and Management

ICANS Assessment and Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; EEG=electroencephalogram; ICANS= immune effector cell-associated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; N/A=not applicable.

Note: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; eg, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS. Grade 5 is considered to be fatal.

[a] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v 5.0, but they do not influence ICANS grading.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Source: (Lee et al., 2019)

10.12 Appendix 12: The Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool

Cognitive Domain	Task	Points	ICE Scoring
Orientation	Orientation to year	1	10: No impairment 7-9: Grade 1 ICANS 3-6: Grade 2 ICANS 0-2: Grade 3 ICANS 0 due to subject unarousable and unable to perform ICE assessment: Grade 4 ICANS
	Orientation to month	1	
	Orientation to city	1	
	Orientation to hospital	1	
Naming	Naming 3 common objects (eg, point to clock, pen, button)	3	
Following commands	Ability to follow simple commands, eg, "Show me two fingers" or "Close your eyes and stick out your tongue"	1	
Writing	Ability to write a standard sentence, eg, "Our national bird is the bald eagle"	1	
Attention	Ability to count backwards from 100 by 10	1	
Maximum ICE Score		10	

Abbreviations: ICANS=immune effector cell-associated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy.
Source: (Lee et al., 2019)

10.13 Appendix 13: Management Guidelines for ICANS

Management Guidelines for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Based on ASTCT Guidelines

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
Grade 1 • ICE score[a] 7-9 and/or depressed level of consciousness[b] but awakens spontaneously • No seizures, motor weakness, or raised ICP/cerebral edema • Confusion: mild disorientation • Encephalopathy: mild limiting of ADLs • Dysphasia: not impairing ability to communicate	• Hold trial treatment until resolution of ICANS. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS • Aspiration precautions • Recommend brain imaging and EEG per institutional guidelines	No concurrent CRS: Anticytokine therapy not indicated Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the ASTCT Guidelines table in Section 10.9. • Consider anakinra as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone, 10 mg IV every 12 hours
Grade 2 • ICE score[a] 3-6 and/or depressed level of consciousness[b] but awakens to voice • No seizures, motor weakness, or raised ICP/cerebral edema • Somnolence-moderate, limiting instrumental ADLs • Confusion: moderate disorientation • Encephalopathy: limiting instrumental ADLs • Dysphasia: moderate impairing ability to communicate spontaneously	• Hold trial treatment until resolution of ICANS. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS (eg, levetiracetam) • Aspiration precautions • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neurologic examinations to include fundoscopy. Consider neurology consult.	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the ASTCT Guidelines table in Section 10.9. • Consider anakinra at a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment.	Dexamethasone at 10-20 mg IV every 12 hours

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
	• Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Prophylactic non-sedating anti-seizure medication	• Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	
Grade 3 • ICE score[a] 0-2 and/or depressed level of consciousness[b] but awakens to tactile stimulus • And clinical seizure focal or generalized that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention • No motor weakness • Focal/local edema on neuroimaging • Somnolence-obtundation or stupor • Confusion: severe disorientation • Encephalopathy: limiting self-care ADLs • Dysphasia: severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	• Hold trial treatment until resolution of ICANS. • Management in monitored care or intensive care unit. • Supportive care per institutional standard of care • Closely monitor neurologic status • Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS (eg, levetiracetam) • Aspiration precautions • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neurologic examinations to include fundoscopy. Consider neurology consult. • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Prophylactic non-sedating anti-seizure medication • Levetiracetam/non-sedating antiepileptics if subject has seizures	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the ASTCT Guidelines table in Section 10.9. • Consider anakinra at a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000 mg/day.
Grade 4 • ICE score[a] 0 and patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma • Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without	• Permanently discontinue trial treatment. • Management in monitored care or intensive care unit. • Supportive care per institutional standard of care • Closely monitor neurologic status	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated: Choose alternative to tocilizumab (eg, siltuximab, anakinra) if possible. (Refer to CRS Management Guidance Based on the	Dexamethasone 10-20 mg IV every 6 hours. If no response, initiate methylprednisolone 1000 mg/day

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids
return to baseline in between • Deep focal motor weakness[c] such as hemiparesis or paraparesis • Diffuse cerebral edema on neuroimaging[d]; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad • Life-threatening consequences • Urgent intervention indicated • Requirement for mechanical ventilation	• Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of ICANS (eg, levetiracetam) • Aspiration precautions • Continuous cardiac telemetry and pulse oximetry as indicated • Closely monitor neurologic status with serial neurologic examinations to include fundoscopy. Consider neurology consult. • Perform brain imaging (eg, MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications • Prophylactic non-sedating anti-seizure medication • Levetiracetam/non-sedating antiepileptics if subject has seizures • Mechanical ventilation may be required • Consider imaging of spine for focal motor weakness • Lower intracranial pressure (ICP) by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema • Aggressive management of ICP with institutional standard of care	ASTCT Guidelines table in Section 10.9. • Consider anakinra at a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	
Grade 5 (Fatal) Death due to ICANS in which another cause is not the principal factor leading to this outcome.			

Abbreviations: ADLs=activities of daily living; ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events; EEG=electroencephalogram; ICANS=immune effector cell-associated neurotoxicity syndrome; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure; IV=intravenous; MRI=magnetic resonance imaging; SC=subcutaneous.

Note: ICANS grade is determined by the most severe domain event not attributable to any other cause. For example, a subject with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

[a] A subject with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.
[b] Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).
[c] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.
[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.
Sources: (Lee et al., 2019)

11 LAY PROTOCOL SYNOPSIS

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

Protocol Title	Efficacy and Safety Study of Acasunlimab as Monotherapy and in Combination With Pembrolizumab in Subjects With Relapsed/Refractory, Unresectable Locally Advanced or Metastatic Cutaneous Melanoma That Progressed On or After Treatment With a Checkpoint Inhibitor	
Brief Title	Study of the Effectiveness and Safety of Acasunlimab Alone or With Pembrolizumab in Treating Advanced Melanoma of the Skin That Returned After or Did Not Respond to Checkpoint Inhibitor Therapy	
Protocol Number	GCT1046-07	
Compound	Acasunlimab (GEN1046; DuoBody®-PD-L1x4-1BB)	
Regulatory Agency Identifier Number(s)	**EU CT No.**	2025-520468-16
	NCT No.	Not available

Brief Summary

The goal of this clinical trial is to learn about the effectiveness and safety of the antibody acasunlimab (also known as DuoBody®-PD-L1x4-1BB) when given either alone or together with the cancer drug pembrolizumab in participants with locally advanced or metastatic melanoma of the skin. All participants will receive active drugs; no one will be given a placebo.

The trial duration will be approximately 15 months for each participant, including a 28-day screening period and estimated 4-month treatment and 10-month follow-up periods; however, the duration of the treatment and follow-up periods may vary for each subject.

Participants will have regular check-ups while on treatment, with visits every week initially, and then every 3 weeks later in the trial.

Rationale

Acasunlimab is an antibody that can bind to 2 different molecules (PD-L1 and 4-1BB) that are present on many cells involved in cancer. Acasunlimab has been investigated in other clinical studies in different solid tumors and has provided benefit to some participants; however, it has not yet been approved for the treatment of any cancer. Pembrolizumab, a type of immunotherapy known as a checkpoint inhibitor, is approved as treatment for patients with unresectable or metastatic melanoma. In clinical studies of acasunlimab in participants with other solid tumors, treatment with acasunlimab in combination with pembrolizumab provided longer lasting benefit than acasunlimab treatment alone.

There is a need for new treatment options that will improve long-term outcomes in patients with previously treated advanced melanoma. Considering the promising results with acasunlimab and acasunlimab in combination with pembrolizumab for the treatment of other solid tumors, this trial will investigate these therapies in participants with advanced melanoma.

The purpose of this trial is to determine the benefit of treatment with acasunlimab alone or in combination with pembrolizumab in participants with locally advanced or metastatic melanoma. The trial will also look at the severity of the possible side effects of these treatments.

Objectives (Purpose) / Endpoints (Assessments)

Primary Objective(s)	**Primary Endpoint(s)**
Evaluate the ability of acasunlimab alone or in combination with pembrolizumab to slow or stop tumor growth, or reduce tumor size	The main trial endpoint is “objective response,” which is a measurement of how the tumor has reacted (shrinkage or growth) to treatment. This endpoint is measured on scans throughout the duration of the trial.
Secondary Objective(s)	**Secondary Endpoints(s)**
Evaluate the time until the tumor shrinks in response to the treatment with acasunlimab alone or in combination with	The secondary trial endpoints are additional ways of measuring a tumor’s response to treatment and the safety of the treatment (these will be measured throughout the duration of the trial):

pembrolizumab and how long the effect lasts.	• Time to response (the time period before tumor shrinkage can be measured) • Duration of response (the time period with tumor shrinkage before tumor growth starts again)
Evaluate how long before the tumor begins to grow and how long participants are alive with acasunlimab treatment alone or in combination with pembrolizumab	• Overall survival is the average length of time subjects are alive after the start of treatment • Progression-free survival is a measure of how stable a subject's cancer is after a certain length of time (no signs of cancer getting worse)
Measure and assess the types and frequency of side effects and tolerability of acasunlimab in combination with pembrolizumab	• How often side effects occur and how serious they are

Trial Population

Participants with locally advanced or metastatic melanoma of the skin who are 18 years of age or older with normal organ and bone marrow function. Participants must have received at least 1 prior treatment, including a checkpoint inhibitor for the treatment of locally advanced or metastatic melanoma. Additional criteria apply that will need to be assessed by the trial team before a decision on trial participation is made.

Ethical Considerations

Results from clinical studies suggest that acasunlimab monotherapy provides early antitumor activity in participants with some advanced solid tumors who were previously treated for their cancer, including with checkpoint inhibitor therapy. In addition, acasunlimab in combination with pembrolizumab demonstrated promising antitumor activity, with longer lasting benefit than acasunlimab alone.

Importantly, clinical studies have shown that side effects related to treatment with acasunlimab and acasunlimab in combination with pembrolizumab are manageable.

Based on available results to date, the possible benefits of treatment with acasunlimab alone and in combination with pembrolizumab outweigh the risks. All the tests and procedures performed throughout the trial are done to ensure the treatments are both safe and effective (that is, the drugs have antitumor activity).

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Protocol Amendment 1 (14 Apr 2025)

Overall Rationale for the Amendment:

To address feedback received from the FDA and align the protocol with standards for the acasunlimab program and Genmab protocols.

Description of Changes:

Section	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Added in criterion 4 and 4a that radiographic progression and BOR assessments are based on RECIST v1.1.	As per request from FDA
6.7.1 Dose Modification Guidance and Discontinuation Criteria for Acasunlimab and Pembrolizumab	Added text on dose modification rules for all AEs.	
6.9 Treatment Beyond Progression	Added text indicating subjects requiring intervention due to rapid disease progression or with signs/symptoms of clinically significant progression are not eligible for treatment beyond progression.	
5.1 Inclusion Criteria	In table for criterion 12, changed"<" to "≤" for serum ALT and AST.	Corrected to align with acasunlimab program standards.
Appendix 6	Updated response criteria in Table 16.	Corrected to align with RECIST v1.1 description in Eisenhauer et al, 2009.
Appendices 8 to 13	Added appendices on classification, grading, and management of various events.	To consolidate guidance on mitigation of these AEs based on acasunlimab experience and align with other acasunlimab trials.
6.1 Investigational and Auxiliary Medicinal Product(s) Table 7, 6.7.1.2.2.1 Cytokine Release Syndrome, 6.7.1.2.2.2 Hemophagocytic Lymphohistiocytosis, 10.2.3.1 Severity	Added reference to grading criteria used for CRS, ICANS, HLH, and/or CTLS.	
Global	Minor editorial updates were made throughout the protocol	To correct typographical, formatting, and/or grammatical errors and align with Genmab protocol standards.

Section	Description of Change	Brief Rationale
Global	Changes made in the body of the protocol are reflected in the synopsis, as applicable.	