Protocol Number:	SGNS40-002
Version:	Amendment 3; 05-Apr-2023
Protocol Title:	An Open-label, Phase 2 Basket Study of SEA-CD40 Combination Therapies in Advanced Malignancies
Investigational Product:	SEA-CD40
Brief Title:	A Study of SEA-CD40 Given with Other Drugs in Cancers
Phase:	2
IND Number:	156290
EudraCT Number:	2021-002037-42
Sponsor:	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Medical Monitor:	PPD , MD Seagen Inc. Tel: PPD Email: PPD
SAE Email or Fax:	See email or fax number specified on the SAE report form.

PROTOCOL SYNOPSIS

Protocol Number	**Product Name**
SGNS40-002	SEA-CD40
Version	**Sponsor**
Amendment 3; 05-Apr-2023	Seagen Inc. 21823 30th Drive SE Bothell, WA 98021, USA
Phase	
2	

Protocol Title

An Open-label, Phase 2 Basket Study of SEA-CD40 Combination Therapies in Advanced Malignancies

Study Objectives

Primary Objective	Corresponding Primary Endpoint
• To evaluate the antitumor activity of SEA-CD40 combined with other therapies	• Confirmed Objective Response Rate (ORR; confirmed complete response [CR] or partial response [PR]) according to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) per investigator assessment
Secondary Objectives	**Corresponding Secondary Endpoints**
• To evaluate the safety and tolerability of SEA-CD40 combined with other therapies	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) • Type, incidence, and severity of laboratory abnormalities • Frequency of treatment interruptions, dose reductions, and treatment discontinuations due to AEs
• To evaluate control of disease	• Disease control rate (DCR; confirmed CR, PR, and stable disease [SD]) per investigator assessment
• To evaluate durability of response in subjects who respond to study drug(s)	• Duration of response (DOR; duration of confirmed CR or PR) per investigator assessment
• To evaluate progression-free survival (PFS) and survival	• PFS per investigator assessment • Overall survival (OS)

Exploratory Objectives	Corresponding Exploratory Endpoints
• To characterize the pharmacokinetics (PK) of SEA-CD40 and incidence of antidrug antibodies (ADAs) when SEA-CD40 is administered in combination with other therapies	• Estimates of selected PK parameters • Incidence of ADAs
Cohorts 1, 2, and 3 (Melanoma): • To evaluate selected pharmacodynamic parameters of interest for SEA-CD40	*Cohorts 1, 2, and 3 (Melanoma):* • Exploratory correlations between QTc and plasma concentrations of SEA-CD40
• To assess exploratory biomarkers of response, toxicity, and resistance of SEA-CD40 in combination with other therapies	• Actual and change from baseline values in immune subsets and cytokines in peripheral blood
• To evaluate the antitumor activity of SEA-CD40 combined with other therapies per Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST)	• Confirmed ORR (immune complete response [iCR] or immune partial response [iPR]) according to iRECIST
• To evaluate patient-reported outcomes of disease/treatment-related symptoms, health-related quality of life (HRQoL), and function	*All Cohorts:* • Actual and change from baseline scores on the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) *Cohorts 4 and 5 only (NSCLC):* • Time-to-deterioration (TTD) in either cough, dyspnea, or chest pain (whichever deteriorates first) as measured by the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) • Actual and change from baseline values in NSCLC-SAQ domains and total scores

Study Population

Eligible subjects are at least 18 years of age with unresectable metastatic cancer. Tumor types evaluated will include relapsed and/or refractory melanoma, uveal melanoma, programmed cell death protein 1 (PD-1) or PD-1 ligand 1 (PD-L1) (PD-(L)1-naive melanoma, and non-squamous non-small cell lung cancer (NSCLC). Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, measurable disease per RECIST v1.1, and adequate baseline laboratory data. Exclusion criteria include, but are not limited to, history of

another malignancy within 3 years, known active central nervous system (CNS) metastases, and previous exposure to CD40-targeted therapy.

Subjects with relapsed and/or refractory melanoma may have received up to 3 prior lines of therapy for advanced disease and must have progressed on treatment with an anti-PD-(L)1 monoclonal antibody (mAb) administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. Subjects with non-uveal/non-ocular relapsed and/or refractory melanoma with a targetable BRAF mutation must have been treated with, been intolerant of, or declined treatment with BRAF/MEK targeted therapy prior to study entry.

Subjects with uveal melanoma must not have received prior treatment for advanced or metastatic disease except adjuvant/neoadjuvant immunotherapy such as interferon, anti-PD-(L)1, or anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) if relapse did not occur during treatment or within 6 months of treatment discontinuation. Subjects with uveal melanoma must have had no prior regional, liver-directed therapy including chemotherapy, radiotherapy, or embolization.

Subjects with PD-(L)1-naive melanoma must not have received prior treatment for advanced or metastatic disease except adjuvant/neoadjuvant immunotherapy such as interferon, anti-PD-(L)1, or anti-CTLA-4 if relapse did not occur during treatment or within 6 months of treatment discontinuation. Subjects with PD-(L)1-naive melanoma and a targetable BRAF mutation may have received prior BRAF/MEK targeted therapy if completed 4 weeks prior to first dose of study drug.

Subjects with non-squamous NSCLC must have stage IV disease per American Joint Committee on Cancer (AJCC) 8th edition, must have no known driver mutations for which targeted therapy is available, and must not have received prior therapy for metastatic disease. Adjuvant/neoadjuvant therapy is allowed for non-metastatic disease if fully completed at least 12 months prior to diagnosis of metastatic disease.

Full eligibility criteria are defined in Section 4.

Number of Planned Subjects

Up to approximately 200 subjects may be enrolled in this study. This includes up to approximately 40 subjects enrolled in each cohort.

Study Design

This phase 2, global, open-label, multicenter trial is designed to assess the activity, safety, and tolerability of SEA-CD40 in combination with standard of care therapies in subjects with selected solid tumors.

Subjects with the following solid tumors will be enrolled:

	Tumor type	Study drugs
Cohort 1	Relapsed/refractory melanoma	SEA-CD40 and pembrolizumab
Cohort 2	Uveal melanoma	
Cohort 3	PD-(L)1-naive melanoma	
Cohort 4	Nonsquamous NSCLC; PD-L1 1%–49% TPS	SEA-CD40, carboplatin, pemetrexed, and pembrolizumab
Cohort 5	Nonsquamous NSCLC; PD-L1 <1% TPS	

A safety monitoring committee (SMC) will monitor the safety of subjects.

For Cohorts 1, 2, and 3 (melanoma), initially, up to 15 subjects may enroll in each cohort. Interim safety and efficacy analyses will be performed for each cohort after 15 subjects have received study drug and are response

evaluable. Cohorts may continue to enroll up to an additional 25 subjects, for a total of up to approximately 40 subjects in each cohort. Due to differences in standard of care, subjects in France will not be enrolled in Cohort 1.

For Cohorts 4 and 5 (NSCLC), initially, 6 total subjects will be enrolled across the 2 cohorts; safety will be assessed after the first treatment cycle. If approved by the SMC, Cohorts 4 and 5 may continue to enroll up to 15 subjects per cohort, followed by continuation to up to 40 total subjects per cohort if appropriate.

Response will be assessed every 6 weeks (Q6W) from the date of first dose for 24 weeks and every 12 weeks thereafter until confirmed disease progression. Diagnostic-quality computed tomography (CT) scans and/or magnetic resonance imaging (MRI) will be performed on the chest and abdomen (and pelvis for Cohorts 1, 2, and 3). Subjects' clinical data must be available for case report form (CRF) source verification. Copies of all tumor images must be made available for review by the sponsor (or its designee) upon request. The sponsor may request that images be sent to a central vendor to be held for later review.

The determination of antitumor activity will be based on objective response rate (ORR) assessments as defined by RECIST version 1.1 and by iRECIST. Treatment decisions by the investigator will be based on iRECIST.

Subjects with unconfirmed progressive disease (PD) per iRECIST (iUPD) may continue study treatment at the discretion of the investigator, with additional consent, if all of the following criteria are met:

- Evidence of clinical benefit, defined as the stabilization or improvement of disease related symptoms, as assessed by the investigator
- No symptoms or signs (including worsening laboratory values) indicating unequivocal disease progression
- No decline in ECOG performance status that can be attributed to disease progression
- No tumor growth at critical anatomical sites (eg, leptomeningeal disease) that cannot be managed and stabilized by protocol--allowed medical interventions prior to repeat dosing

Investigational Product, Dose, and Mode of Administration

Cohorts 1, 2, and 3 (Melanoma)

SEA-CD40 will be administered as an intravenous (IV) infusion at a dose of 10 mcg/kg on Day 1 and Day 22 of each 42 -day cycle.

Pembrolizumab will be administered IV on Day 8 of each 42-day cycle. The dose of pembrolizumab is the standard approved dose of 400 mg Q6W for approved indications.

Cohorts 4 and 5 (NSCLC)

SEA-CD40 will be administered as an IV infusion at a dose of 10 mcg/kg on Day 3 of each 21-day cycle.

Pembrolizumab will be administered IV on Day 1 of each 21-day cycle. The dose of pembrolizumab is the standard approved dose of 200 mg every 3 weeks (Q3W) for approved indications.

Pemetrexed will be administered on Day 1 of each 21-day cycle at a dose of 500 mg/m^2.

Carboplatin will be administered on Day 1 of Cycles 1 to 4 at a dose of area under the concentration-time curve (AUC) 5 mg per milliliter per minute.

Duration of Treatment

Subjects who achieve stable disease (SD) or better may continue study treatment for approximately 2 years or until unacceptable toxicity, confirmed disease progression, withdrawal of consent, or study termination, whichever occurs first.

Pembrolizumab administration will be discontinued once the subject has completed approximately 2 years with pembrolizumab (35 administrations Q3W or 18 administrations Q6W).

Antitumor Activity Assessments

Antitumor activity will be assessed by radiographic tumor imaging at protocol-specified time points. Response assessment for primary and secondary efficacy endpoints will be evaluated by the investigator using RECIST v1.1. Subjects will be followed for response assessments until disease progression, subsequent cancer therapy, study termination by the sponsor, or death, whichever comes first.

Pharmacokinetic and Immunogenicity Assessments

Blood plasma samples for pharmacokinetics (PK) and serum samples for antidrug antibodies (ADA) assessments of SEA-CD40 will be collected at protocol-defined time points. PK parameters to be estimated include, but are not limited to, AUC and maximum concentration (C_{max}).

Pharmacodynamic Assessments

In Cohorts 1, 2, and 3 only, the correlation between QTc and plasma concentrations of SEA-CD40 will be assessed.

Biomarker Assessments

Peripheral blood and tumor tissue will be collected at protocol-specified time points. Exploratory, predictive, and prognostic biomarkers associated with response, resistance, or safety observations will be monitored before and during treatment with SEA-CD40. These collections may be discontinued at the discretion of the sponsor.

To characterize the malignancy and response to study treatment, biomarker assessments in tumor biospecimens may include, but are not limited to, characterization of the tumor microenvironment, PD-L1 expression, drug target(s), tumor subtyping, profiling of somatic mutations and/or gene expression. Assays may include, but are not limited to, immunohistochemistry (IHC) and next generation sequencing of RNA and DNA.

To characterize the malignancy and immune response, biomarker assessments in peripheral blood may include, but are not limited to, measurement of baseline and drug-induced changes in circulating blood cell populations, cytokines/chemokines, gene expression, cytogenetics, genetic polymorphisms, somatic mutations associated with cancer, and circulating immune function and disease markers. Assays may include, but are not limited to, next generation sequencing of whole blood, proteomic methodologies, immunoassays as a marker of tumor response or therapy resistance, and markers of immune function, including abundance of immune cell subsets and cytokines. Methods of analysis may include, but are not limited to, immunoassays such as flow cytometry and enzyme-linked immunosorbent assays (ELISA).

Safety Assessments

Safety assessments will include the surveillance and recording of adverse events (AEs) including serious adverse events (SAEs), recording of concomitant medication, and measurements of protocol-specified physical examination findings, vital signs, protocol-specified laboratory tests, ECOG status, electrocardiograms (ECGs), and pregnancy testing.

Patient-Reported Outcome Assessments

Patient-reported outcome (PRO) assessments will only be administered to subjects entered in the study after completion of enrollment for the interim analysis in each cohort.

All Cohorts

To assess PROs of disease/treatment-related symptoms, health-related quality of life (HRQoL), and function, the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) will be administered to subjects at baseline, every 21 days (Q21d) during treatment cycles, and at the end of treatment (EOT) visit. PRO collections may be discontinued at the discretion of sponsor. Cohorts 4 and 5 only (NSCLC)

The NSCLC—SAQ will be used to assess severity of the following NSCLC symptoms: cough, pain, dyspnea, fatigue, and appetite. The NSCLC—SAQ will be administered at baseline, on Day 1 of each treatment cycle, and the EOT visit. The Patient Global Impression scales of symptom severity (PGI—S) and symptom change (PGI—C) will also be included. The PGI-S will be administered at baseline and at the EOT visit. The PGI-C will be administered on Day 1 of Cycle 2 and beyond.

Scores will be calculated based on the respective instruments' scoring manuals.

Statistical Methods

The primary analysis of the study will be performed separately for each cohort when all treated subjects in the cohort have been followed for at least 6 months or come off study, whichever comes first. The primary efficacy endpoint of confirmed ORR per RECIST v1.1 will be estimated for each cohort based on the response evaluable analysis set, comprising subjects with measurable disease at baseline who received any amount of study treatment and had at least 1 postbaseline disease assessment per RECIST or discontinued study treatment. The point estimate of ORR and 95% exact confidence intervals (CIs) using the Clopper-Pearson method will be provided for each cohort.

Interim futility analyses will be performed separately for each cohort after approximately 15 subjects of a given cohort have been treated and are response evaluable. The Bayesian predictive probability of success (PpoS) approach will be used to inform decision-making for continued enrollment. A cohort is considered "successful" if the 90% CI of the response rate at the maximum sample size excludes the background rate. At the time of each interim analysis, the PpoS will be calculated. A PpoS <5% indicates that it is unlikely the ORR will be better than the response rate of current standard of care at the end of the cohort given the interim result. Based on efficacy and safety data, together with the PpoS, a cohort may be stopped early by the sponsor. A cohort may also be discontinued at any point at the discretion of the sponsor.

Safety measurements will be summarized by descriptive statistics based on the safety analysis set. The safety analysis set will include all subjects who received any amount of study treatment.

PRO outcomes endpoints will be summarized using descriptive statistics. Time-to-deterioration (TTD) analyses will also be performed for the NSCLC-SAQ questionnaire.

For a sample size of 40 subjects per cohort, assuming confirmed ORR is between 30% and 80%, the 2-sided 95% exact CI are summarized below:

Confirmed ORR	95% Exact CI (N=40)
30%	(17%, 47%)
40%	(25%, 57%)
50%	(34%, 66%)
60%	(43%, 75%)
70%	(53%, 83%)
80%	(64%, 91%)

SCHEDULE OF EVENTS

Table 1: Schedule of Events for Cohorts 1, 2, and 3 (Melanoma)

		Screening/Baseline		Enrollment	Every 42-day cycle				EOT	Follow-up	Survival follow-up
	Day	D –28 to 1	D –7 to 1 (unless otherwise stated)	Within 7D of 1st dose	D1	D8	D22	D36	Within 30–37D of last dose[A]	Every 12 wks (unless otherwise stated)	Every 12 wks (unless otherwise stated)
	Visit window				±2d	±2d	±2d	-2 d/+5 d		±1 wk	±1 wk
Screening/ Baseline Assessments	Inclusion/Exclusion, medical history	X		Submit eligibility confirmation to Sponsor prior to treatment	Cycle 1[B]						
	Informed consent	X									
	MRI of brain[C]	X									
Safety Assessments	Urinalysis, including UPC ratio		X		X[D]						
	Pregnancy test (subjects of childbearing potential)		X[E]		X[F]		X[G]		X	X[H]	
	Physical examination		X		X[I]				X	X	
	Weight		X		X[I]				X		
	Height (height measured within the prior 12 months may be utilized)	X									
	CBC with differential		X		X[I]	X[U]	X[I]		X		
	Chemistry panel		X		X[I]	X[U]	X[I]		X	X (at first FU only)	
	Thyroid panel	X			X[I]				X	X (at first FU only)	
	Hgb A1c	X							X		
	Vital signs		X		X	X[J]	X		X		
	PT/aPTT/INR[K]		X						X		
	ECG performance status		X		X[I]				X		
	ECG	X			See Table 4 for on-treatment ECG time points (first 30 subjects only)				X		

		Screening/Baseline		Enrollment	Every 42-day cycle				EOT	Follow-up	Survival follow-up
	Day	D –28 to 1	D –7 to 1 (unless otherwise stated)	Within 7D of 1st dose	D1	D8	D22	D36	Within 30–37D of last dose[A]	Every 12 wks (unless otherwise stated)	Every 12 wks (unless otherwise stated)
	Visit window				±2d	±2d	±2d	-2 d/+5 d		±1 wk	±1 wk
	Concomitant medications	Related to study procedures[L]			Collect from Day 1 predose through safety reporting period of study drug(s)						
	AE collection									X[M]	
Treatment	SEA-CD40 administration				X		X				
	Pembrolizumab administration					X					
PK/Immunogenicity / Biomarker	Initiate retrieval of archived tumor specimen		X								
	Tumor biopsy (FFPE)[N]	X[O]						Cycle 1[P]			
	Blood sample collection	See Table 3 for sample collection details. Note sample collections on **Day 2 of Cycles 1 and 2.**									
Response Assessment	CT or MRI of chest, abdomen, pelvis (and neck and/or brain if documented or suspected involvement)[Q]	X			X[R]				X[S]	X[T]	
	Disease and survival status[U]									X	X
PRO Assessments	EORTC QLQ-C30		X[V]		X				X		

AE=adverse event; CBC=complete blood count; CT=computed tomography; D=day; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EORTC QLQ-Q30=European Organization for Research and Treatment of Cancer quality of life questionnaire; EOT=end of treatment; FFPE=formalin-fixed paraffin embedded; FU=follow-up; Hgb=hemoglobin; MRI=magnetic resonance imaging; PK=pharmacokinetic; PRO=patient-reported outcome; PT/aPTT/INR=prothrombin time/activated partial thromboplastin time/international normalized ratio; UPC=urine protein creatinine; wk=week

A EOT evaluations must be obtained before the initiation of non-protocol anticancer treatment. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

B Confirm eligibility prior to assessments and dosing on Cycle 1 Day 1.

C If an MRI of the brain is medically contraindicated, CT with contrast is an acceptable alternative.

D Urinalysis should be conducted every 3 cycles starting in Cycle 3. May be collected within 3 days prior to dosing.

E Collect on Study Day –3 to 1.

F In Cycle 1, not required if performed within 3 days prior to visit. In all other cycles, not required if performed within 7 days prior to visit.

G Not required if performed within 7 days prior to dosing.

H After the last dose of study drug, pregnancy tests will be performed once a month for 120 days or per local regulations, where applicable. Subjects may do monthly home pregnancy tests and report interim results at the follow-up visits.

I May be collected within 3 days prior to dosing.

J Collect prior to pembrolizumab administration.

K Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial as clinically indicated.

L From time of informed consent.

M Collect AEs if serious for 90 days after the last study treatment and immune-related adverse events (irAEs) through the first follow-up visit. If a subject starts a new anticancer therapy, collection of serious adverse events (SAEs) that are not related to study treatment and irAEs may be stopped 30 days after the cessation of study treatment (see Section 7.7.1.3 for details). Study treatment-related SAEs that occur after the safety reporting period should also be reported to the sponsor.

N If a tumor sample is obtained as part of standard of care during the study, a part of that sample should be submitted to the sponsor if available.

O If archived tumor specimen is not available, fresh tumor biopsy is required. For subjects who will have an on-treatment biopsy, a fresh baseline biopsy is required if archival sample collected within 30 days prior to anticipated first dose of study drug is not available (see Section 7.4 for details)

P Required for subjects enrolled after completion of enrollment for the interim analysis in Cohorts 1 and 2. Optional for all other subjects. The same tumor site should be biopsied at baseline and on treatment if possible (see Section 7.4 for details)

Q For each assessed lesion, the same modality should be used throughout the duration of the study.

R Response should be assessed by CT or MRI every 6 weeks (± 3 days) from Cycle 1 Day 1 regardless of dose delays for 24 weeks and every 12 weeks (±1 week) thereafter.

S Not required if conducted 4 weeks prior to EOT.

T Response assessments will continue until disease progression (iCPD per iRECIST), initiation of new anticancer therapy, study termination by the sponsor, or death, whichever comes first.

U After disease progression or initiation of new anticancer treatment, follow-up for disease and survival status, and subsequent anticancer treatment information until death or study closure. Assessment of survival can be done via public or hospital/medical records or a phone call.

V Patient reported outcome (PRO) assessments will only be administered to subjects entered in the study after completion of enrollment for the interim analysis in each cohort. All PRO assessments should be completed by the subject prior to discussion of the subject's health state, lab results, health record, and prior to any study drug administration or other study assessment.

Note: Each time a subject discontinues a component of combination therapy but is continuing with another component, clinic visits and safety assessments (including pregnancy testing) associated with the discontinued treatment may be moved or eliminated (if considered appropriate after consultation with the medical monitor), if there are no other study drugs administered on that day. If biomarker/PRO assessments fall on a day that no longer has any study drug administered, these may be moved to the next scheduled visit or eliminated, if considered appropriate after consultation with the medical monitor. PRO collections may be discontinued at the discretion of sponsor.

Note: Subjects in France will not be enrolled in Cohort 1.

Table 2: Schedule of Events for Cohorts 4 and 5 (NSCLC)

		Screening/ Baseline		Enrollment	Every 21-day cycle			EOT	Follow-up	Survival follow-up
	Day	D –28 to 1	D –7 to 1 (unless otherwise stated)	Within 7D of 1st dose	D1	D3	D15	Within 30–37D of last dose[A]	Every 12 wks (unless otherwise stated)	Every 12 wks (unless otherwise stated)
	Visit window				±2d		-2d/+5d		±1 wk	±1 wk
Screening/ Baseline Assessments	Inclusion/Exclusion, medical history	X		Submit eligibility confirmation to Sponsor prior to treatment	Cycle 1[B]					
	Informed consent	X								
	MRI of brain[C]	X								
Safety Assessments	Urinalysis, including UPC ratio		X		X[D]					
	Pregnancy test (subjects of childbearing potential)		X[E]		X[F]			X	X[G]	
	Physical examination		X		X[H]			X	X	
	Weight		X		X[H]			X		
	Height (height measured within the prior 12 months may be utilized)	X								
	CBC with differential		X		X[H]	X		X		
	Chemistry panel		X		X[H]	X		X		
	Hgb A1c	X						X		
	Thyroid panel	X			X[H,I]			X	X (at first FU only)	
	Vital signs		X		X	X		X	X (at first FU only)	
	PT/aPTT/INR[J]		X					X		
	ECOG performance status		X		X[H]			X		
	ECG	X						X		
	Concomitant medications	Related to study procedures[K]								

		Screening/ Baseline		Enrollment	Every 21-day cycle			EOT	Follow-up	Survival follow-up
	Day	D –28 to 1	D –7 to 1 (unless otherwise stated)	Within 7D of 1st dose	D1	D3	D15	Within 30–37D of last dose[A]	Every 12 wks (unless otherwise stated)	Every 12 wks (unless otherwise stated)
	Visit window				±2d		-2d/+5d		±1 wk	±1 wk
	AE collection				Collect from Day 1 predose through safety reporting period of study drug(s)				X[L]	
Treatment	SEA-CD40 administration					X				
	Pembrolizumab administration				X					
	Pemetrexed administration				X[M]					
	Carboplatin administration				Cycles 1–4					
PK/Immunogenicity /Biomarker	Initiate retrieval of archived tumor specimen[N]		X							
	Tumor biopsy (FFPE)[O]	X[N]					Cycle 2[P]			
	Blood sample collection	See Table 5 for sample collection details. Note sample collections on **Day 4 of Cycles 1 and 2.**								
Response Assessment	CT or MRI of chest and abdomen, (and pelvis, neck, and/or brain if documented or suspected involvement)[Q]	X			X[R]			X[S]	X[T]	
	Disease and survival status[U]								X	X
PRO Assessment	EORTC QLQ-C30		X[V]		X			X		
	NSCLC-SAQ		X[V]		X			X		
	PGI-S		X[V]					X		
	PGI-C				X[W]					

AE=adverse event; CBC=complete blood count; CT=computed tomography; D=day; ECOG=Eastern Cooperative Oncology Group; ECG=electrocardiogram; EOT=end of treatment; FFPE=formalin-fixed paraffin embedded; FU=follow-up; Hgb=hemoglobin; MRI=magnetic resonance imaging; PK=pharmacokinetic; PRO=patient-reported outcome; PT/aPTT/INR=prothrombin time/activated partial thromboplastin time/international normalized ratio; UPC=urine protein creatinine; wk=week

A EOT evaluations should be obtained before the initiation of non-protocol anticancer treatment. If EOT evaluations are completed before 30 days following the last study treatment, conduct a phone screen 30–37 days following the subject's last study treatment to ensure that no changes in AE profile have occurred.

B Confirm eligibility prior to assessments and dosing on Cycle 1 Day 1.

C If an MRI or the brain is not medically feasible, CT may be used.

D Urinalysis should be conducted every 6 cycles starting in Cycle 6. May be collected within 3 days prior to dosing.
E Collect on Study Day –3 to 1.
F In Cycle 1, not required if performed within 3 days prior to visit. In all other cycles, not required if performed within 7 days prior to visit.
G After the last dose of study treatment, pregnancy tests will be performed once a month for 6 months, or per local regulations, where applicable. Subjects may do monthly home pregnancy tests and report interim results at the follow-up visits.
H May be collected within 3 days prior to dosing.
I Cycle 1 and every second cycle thereafter
J Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial as clinically indicated.
K From time of informed consent.
L Collect Aes if serious for 90 days after the last study treatment and immune-related adverse events (irAEs) through the first follow-up visit. If a subject starts a new anticancer therapy, collection of serious adverse events (SAEs) that are not related to study treatment and irAEs may be stopped 30 days after the cessation of study treatment (see Section 7.7.1.3 for details). Study treatment-related SAEs that occur after the safety reporting period should also be reported to the sponsor.
M See Section 5.3 regarding corticosteroid and anti-emetic prophylaxis.
N If archived tumor specimen is not available, fresh tumor biopsy is required (see Section 7.4 for details). Collection of fresh biopsies may be stopped at the discretion of the sponsor.
O If a tumor sample is obtained as part of standard of care during the study, a part of that sample should be submitted to the sponsor if available.
P On-treatment biopsy is optional.
Q For each assessed lesion, the same modality should be used throughout the duration of the study.
R Response should be assessed by CT every 6 weeks (± 3 days) from Cycle 1 Day 1 regardless of dose delays for 24 weeks and every 12 weeks (±1 week) thereafter.
S Not required if conducted 4 weeks prior to EOT.
T Response assessments will continue until disease progression (iCPD per iRECIST), initiation of new anticancer therapy, study termination by the sponsor, or death, whichever comes first.
U After disease progression or initiation of new anticancer treatment, follow-up for disease and survival status, and subsequent anticancer treatment information until death or study closure. Assessment of survival can be done via public or hospital/medical records or a phone call.
V Patient-reported outcome (PRO) assessments will only be administered to subjects entered in the study after completion of enrollment for the interim analysis in each cohort. All PRO assessments should be completed by the subject prior to discussion of the subject's health state, lab results, health record, and prior to any study drug administration or other study assessment. PRO collections may be discontinued at the discretion of sponsor.
W Not required in Cycle 1. PGI-C should be administered from Cycle 2 onward.
Note: Each time a subject discontinues a component of combination therapy but is continuing with another component, clinic visits and safety assessments (including pregnancy testing) associated with the discontinued treatment may be moved or eliminated (if considered appropriate after consultation with the medical monitor), if there are no other study drugs administered on that day. If biomarker/PRO assessments fall on a day that no longer has any study drug administered, these may be moved to the next scheduled visit or eliminated, if considered appropriate after consultation with the medical monitor.

BIOMARKER AND ECG COLLECTIONS

Table 3: Biomarker Collections for Cohorts 1, 2, and 3 (Melanoma)

Cycle	Study Day	Time	Collection Window	Relative Time	SEA-CD40 PK	SEA-CD40 ADA	Serum	PBMC	Plasma	cfDNA	PD Flow[A]	Genotyping
Day –7 to –1							X	X	X		X	X
Cycle 1 and 2	Day 1	Predose SEA-CD40[B]	within 4 hrs prior to	Start of SEA-CD40 infusion	X[C]	X	X	X	X	X	X	
		1 hr intra-dose[B,D,E]	±15 min	1 hour after start of SEA-CD40 infusion	X							
		2 hrs intra-dose[B,D,F]	±15 min	2 hours after start of SEA-CD40 infusion	X							
		End of SEA-CD40 infusion	within 30 min	End of SEA-CD40 infusion	X[C]				X			
		2 hrs	±15 min		X				X			
	Day 2	24 hrs[B]	±4 hr	Start of SEA-CD40 infusion	X[C]				X		Cycle 1	
	Day 22	Predose SEA-CD40[B]	within 4 hrs prior to	Start of SEA-CD40 infusion	X	X			X			
		End of SEA-CD40 infusion	within 15 min	End of SEA-CD40 infusion	X							
All other cycles	Day 1	Predose SEA-CD40[B]	within 24 hrs	Start of SEA-CD40 infusion	X	X	Cycles 3–4	Cycles 3–4	X		Cycles 3–6	
EOT	30–37 days after last study drug[G]				X	X	X	X	X	X		

ADA=antidrug antibody; cfDNA=cell-free DNA; EOT=end of treatment; ECG=electrocardiogram; hr(s) = hour(s); min(s)=minutes(s); PBMC=peripheral blood mononuclear cell; PD=pharmacodynamic; PK=pharmacokinetic; PRO=patient reported outcomes

A Blood samples for PD flow should be collected in Cohorts 1 and 2 from subjects enrolling before the first interim analysis at US sites only.

B The time noted is relative to the start of the SEA-CD40 infusion.

C For the first 30 subjects across Cohorts 1, 2, and 3, ECGs should be performed within 30 minutes prior to PK sample collection at these time points. (see Table 4)

D Blood samples collected during the SEA-CD40 infusion should be obtained from the contralateral arm, or another site other than the infusion line.

E Collect 1 hr intra-dose sample if SEA-CD40 infusion time exceeds 1 hour if collection window does not overlap with end of infusion.

F Collect 2 hr intra-dose sample if SEA-CD40 infusion time exceeds 2 hours if collection window does not overlap with end of infusion.

G EOT samples must be collected before initiation of a new anticancer treatment (see Section 6.4).

Note: If collection kits are unavailable on the intended collection day, the sample collection may be omitted in consultation with the sponsor.

Note: Subjects in France will not be enrolled in Cohort 1.

Note: Any samples and data collection for exploratory objectives which are not necessary to evaluate any primary and secondary objective can be discontinued at the discretion of the sponsor (for example, but not limited to: PROs, SEA-CD40 PK, CD40 ADA, Plasma, PD flow, Tumor biopsy, Genotyping, Serum, PBMC, cfDNA).

Table 4: ECG Collections for Cohorts 1, 2, and 3 – Up to 30 Subjects in Total (US sites only)

Cycle	Study Day	Time	Relative Time	ECG
Cycles 1 and 2	Day 1	Predose	START of SEA-CD40 infusion	X
		30 minutes post end of infusion	END of SEA-CD40 infusion, within 30 minutes prior to postdose PK blood draw	X
		2 hours	END of SEA-CD40 infusion, prior to 2-hour PK blood draw	X
	Day 2	24 hours	START of infusion, within 30 minutes prior to 24-hour PK blood draw	X

ECG=electrocardiogram; PK=pharmacokinetic

Note: ECGs should be performed within 30 minutes prior to PK sample collection at corresponding time points. On-treatment ECGs should be performed for up to approximately 30 subjects at US sites across Cohorts 1, 2, and 3.

Table 5: Biomarker Collections for Cohorts 4 and 5 (NSCLC)

Cycle	Study Day	Time	Collection Window	Relative Time	SEA-CD40 PK	SEA-CD40 ADA	Serum	PBMC	Plasma	cfDNA	PD Flow[A]	Genotyping
Day –7 to –1							X	X	X		X	X
Cycles 1 and 2	Day 1	Predose chemo and pembrolizumab (-48 hr)[B,C]	within 4 hrs prior to	Start of pembrolizumab infusion			X	X	X	X	X	
	Day 3	Predose SEA-CD40 (0 hr)	within 4 hrs prior to	Start of SEA-CD40 infusion	X	X			X		Cycle 1	
		1 hr intra-dose[B,D,E]	±15 min	1 hour after start of SEA-CD40 infusion	X							
		2 hrs intra-dose[B,D,F]	±15 min	2 hours after start of SEA-CD40 infusion	X							
		End of SEA-CD40 infusion	within 15 min	End of SEA-CD40 infusion	X				X			
		2 hrs	±15 min	2 hours after end of SEA-CD40 infusion	X				X			
	Day 4	24 hrs[B]	within 4 hrs prior to	Start of SEA-CD40 infusion	X				X		Cycle 1	
Cycles 3, 4, 6, and 8	Day 1	Predose chemo and pembrolizumab (–48 hr)[B]	within 4 hrs prior to	Start of pembrolizumab infusion	X	X	Cycles 3–4	Cycles 3–4	X		X	
EOT	30–37 days after last study drug[G]				X	X	X	X	X	X		

ADA=antidrug antibody; EOT=end of treatment; ECG=electrocardiogram; hr(s) = hour(s); min(s)=minutes(s); PBMC=peripheral blood mononuclear cell; PD=pharmacodynamic; PK=pharmacokinetic; PRO=patient reported outcomes

A Blood samples for PD flow should be collected from subjects enrolling before the first interim analysis at US sites only.

B The time noted is relative to the start of the SEA-CD40 infusion.

C Collect pre-dose samples prior to administering pre-medication.

D Blood samples collected during the SEA-CD40 infusion should be obtained from the contralateral arm, or another site other than the infusion line.

E Collect 1 hr intra-dose sample if SEA-CD40 infusion time exceeds 1 hour if collection window does not overlap with end of infusion.

F Collect 2 -hr intra-dose sample if SEA-CD40 infusion time exceeds 2 hours if collection window does not overlap with end of infusion.

G EOT samples must be collected before initiation of a new anticancer treatment (see Section 6.4).

Note: If collection kits are unavailable on the intended collection day, the sample collection may be omitted in consultation with the sponsor

Note: Any samples and data collection for exploratory objectives which are not necessary to evaluate any primary and secondary objective can be discontinued at the discretion of the sponsor (for example, but not limited to: PROs, SEA-CD40 PK, CD40 ADA, Plasma, PD flow, Tumor biopsy, Genotyping, Serum, PBMC, cfDNA).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	antidrug antibody
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic large-cell lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
β-hCG	beta human chorionic gonadotropin
C_{max}	maximum concentration
C_{trough}	trough concentration
CBC	complete blood count
cfDNA	cell-free DNA
CI	confidence interval
CNS	central nervous system
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DC	dendritic cells
DCR	disease control rate
DILI	drug-induced liver injury
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGRF	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
EOT	end of treatment
ePRO	electronic patient-reported outcome
FAS	full analysis set
FFPE	formalin-fixed paraffin-embedded
FU	follow-up
HNSCC	head and neck squamous cell carcinoma
HNSTD	highest non-severely toxic dose

HRQoL	health-related quality of life
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICD	immunogenic cell death
ICH	International Council for Harmonisation
iCPD	confirmed progressive disease per iRECIST
iCR	immune complete response
IEC	independent ethics committee
Ig	immunoglobulin
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4
IgV	immunoglobulin V
IHC	immunohistochemistry
IHR	infusion or hypersensitivity reaction
IND	investigational new drug
iPR	immune partial response
IRB	institutional review board
irAE	immune-related AEs
iRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRR	infusion-related reaction
iUPD	immune unconfirmed progressive disease
IV	intravenous(ly)
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer [cells]
NOAEL	no observed adverse effects level
NSAIDS	non-steroid anti-inflammatory drugs
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire

ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PBPK	physiologically-based PK
PCR	polymerase chain reaction
PD	progressive disease
PD	pharmacodynamics
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-(L)1	programmed cell death protein 1 (PD-1) or PD-1 ligand 1 (PD-L1)
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PGI-C	Patient Global Impression of Symptom Change
PGI-S	Patient Global Impression of Symptom Severity
PK	pharmacokinetics
PpoS	predictive probability of success
PR	partial response
PRO	patient-reported outcomes
PT/aPTT/INR	prothrombin time/activated partial thromboplastin time/international normalized ratio
Q2W	every 2 weeks
Q3W	every 3 weeks
Q3Wx5	every 3 weeks five times
Q6W	every 6 weeks
Q21d	every 21 days
Q42d	every 42 days
RE	response evaluable analysis set
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SD	stable disease
SMC	Safety Monitoring Committee
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TPS	tumor proportion score

TTD	time-to-deterioration
ULN	upper limit of normal
UPC	urine protein creatinine ratio
USP	United States Pharmacopeia
USPI	United States Prescribing Information
wk	week

1. INTRODUCTION

A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the SEA-CD40 Investigator's Brochure (IB).

1.1. CD40

One widely expressed stimulatory receptor, CD40, is a member of the tumor necrosis factor (TNF) receptor superfamily and is normally expressed and utilized by the immune system. CD40 is expressed by antigen-presenting cells (APCs), including dendritic cells (DCs), B cells, macrophages and monocytes (Gruss 1997; van Kooten 1997). It is also expressed on several types of B-cell neoplasms, including non-Hodgkin lymphoma, multiple myeloma, chronic lymphocytic lymphoma, Waldenström's macroglobulinemia, and Hodgkin lymphoma, as well as on a significant percentage of solid tumors, including melanoma and other carcinomas (ie, pancreatic, lung, ovarian, bladder, breast, colon, and prostatic) (Carbone 1996; Wingett 1998; Cooke 1999; Ottaiano 2002; Kim 2003; Tong 2003).

1.2. Role of CD40 in Cancer

CD40 binds to CD40 ligand (CD40L, CD154), which is transiently expressed on activated T cells, and at variable levels on monocytes, activated B cells, epithelial and vascular endothelial cells, smooth muscle cells, and DCs. Such interactions lead to cognate, antigen-driven B- and T-cell activation and differentiation (van Kooten 2000; Elgueta 2009). CD40 activation has been specifically demonstrated to evoke tumor-specific cytotoxic T-cell responses, likely in part by inducing and/or enhancing adhesion proteins like CD54, co-stimulatory molecules like CD86 and major histocompatibility complex (MHC) antigens on APCs, including DCs, suggesting its value as an oncology therapeutic target (French 1999; Kurts 2010; Gajewski 2013).

A number of CD40-directed antibodies have been developed, all of which have elicited some clinical activity in both hematologic and solid malignancies (Hassan 2014). CD40-directed antibodies that have been studied in the clinic include Chi Lob 7/4 (Johnson 2013), lucatumumab (Bensinger 2012; Byrd 2012; Fanale 2014), CP-870,893 (Ruter 2010; Beatty 2013; Vonderheide2013b), and in particular, dacetuzumab (Advani 2009; Furman 2010; Hussein2010; Burington 2011; Forero-Torres 2013; de Vos 2014).

1.3. Tumor Immunology: Immune Evasion Versus Activation

Much attention has focused on mechanisms of immune system evasion by tumors, such as the exploitation of the cytotoxic T-lymphocyte-associated protein 4 (CTLA4)-CD80/CD86 and programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) (together referred to as PD-(L)1 hereafter) inhibitory systems. As demonstrated in clinical studies of monoclonal antibodies against CTLA4 or PD-1 (called checkpoint inhibitors), dysregulation of inhibitory receptors by tumors and/or their environments results in relative immune suppression or inhibition (Hodi 2010; Topalian 2012; Hamid 2013). However, defective immune stimulation or activation has also been considered to contribute to tumor pathogenesis, leading to the advent of immunostimulatory approaches to cancer treatment, such as chimeric antigen receptor (CAR) T cells (Kershaw 2013) or the cancer vaccine sipuleucel-T for prostate cancer (Kantoff 2010). In this regard, several other immune pathways may provide targets for immunostimulatory therapeutic intervention, including activation of APCs, to promote tumor antigen-specific T-cell

responses. Many novel investigational therapies for cancer have therefore pursued several monoclonal antibody (mAb) targets in co-stimulatory and inhibitory systems, such as novel B7 ligands, CD27, 4-IBB (CD137), LAG3 (CD223), 2B4 (CD244), TIM3, or BTLA (CD272) (Mellman 2011; Pardoll 2012).

1.4. Description of SEA-CD40

To improve upon the biologic activity of dacetuzumab, SEA-CD40 has been generated as a nonfucosylated derivative. It has the same amino acid sequence and is produced by adding the fucosylation inhibitor 2-fluorofucose during manufacture of dacetuzumab. SEA-CD40 demonstrates significantly superior binding to both high- and low-affinity allelic variants of FcγRIIIa, resulting in more potent antibody-dependent cellular cytotoxicity (ADCC) activity against both a CD40-positive lymphoma B-cell line and normal B cells. Additionally, this increased FcγRIIIa binding results in enhanced agonistic signaling to APCs as demonstrated by pro-inflammatory cytokine secretion and induction of immune co-stimulatory receptors such as CD80, CD86, and MHC Class I and II antigens (MHCI and MHCII). In this way, SEA-CD40 is expected to accentuate immune activation more potently by priming naive CD4+ and CD8+ T cells to differentiate into helper and cytotoxic T cells, respectively, and furthermore to promote the secretion of pro-inflammatory cytokines, leading to the activation of natural killer (NK) cells as well as further activation of APCs. Direct engagement of CD40 on tumor cells may promote local immune activation and exert direct anti-proliferative effects. SEA-CD40 may therefore confer multiple beneficial anti-tumor mechanisms superior to other CD40-directed therapies, including dacetuzumab (Hassan 2014).

1.5. SEA-CD40 Mechanism of Action

CD40 is a widely expressed member of the TNF receptor superfamily found on the surface of myeloid cells. As a TNF family member, CD40 activation requires clustering of the receptor on the cell surface in a process known as agonism. CD40 agonism results in induction of cytokines and chemokines and up-regulates co-stimulatory receptors on innate cells in a way that promotes the transformation of naive CD8+ T cells into antigen experienced memory CD8+ T cells.

SEA-CD40 is a nonfucosylated antibody that binds with high affinity to CD40 and FcγRIIIa while avoiding binding to the inhibitory FcγRIIb receptor. Agonism of CD40 is facilitated by IgG1 antibodies concomitant binding to CD40 on myeloid cells and Fc receptors expressed on immune effector cells, eg, NK and myeloid cells. There are 2 types of Fc receptors, those that that activate (FcγRIIIa, FcγRIIa, FcγRI) or those that suppress (FcγRIIb) myeloid cell functionality. SEA-CD40 induces innate cell activation in 2 complimentary ways; one by facilitating the clustering and agonism of CD40 and the other by driving a positive activating signal through FcγRIIIa. SEA-CD40 confers anti-tumor activity by activating innate cells in a specific way, which drives antigen specific memory CD8+ T-cell responses.

1.6. Summary of Nonclinical Toxicity

The toxicity of SEA-CD40 has been evaluated in exploratory and Good Laboratory Practice-compliant studies in cynomolgus monkeys at dose levels 0.03 to 30 mg/kg administered intravenously (IV) as either single or repeat doses (Q3Wx5). SEA-CD40-related findings were limited to changes in clinical observations, hematology, clinical chemistry, ophthalmology, flow cytometry, cytokines, organ weights, histopathology, immunohistochemistry (IHC),

toxicokinetics, and immunogenicity. No treatment-related findings were observed in body weights, food consumption, coagulation, urinalysis, respiratory rate, heart rate, blood pressure, body temperature, electrocardiograms (ECGs), neurological exams, menstrual cycles, male reproductive endpoints, or T-lymphocyte proliferation following administration of SEA-CD40 at up to 30 mg/kg. Overall, the most prominent effects observed were infusion-related reactions, increased cytokine production, decreases in lymphocytes in the periphery and spleen, thymus and lymph nodes, thrombocytopenia, transient liver enzyme (alanine aminotransferase [ALT]) elevation, and vascular/perivascular infiltrates in multiple tissues. In addition, 1 animal treated with a single dose of 30 mg/kg SEA-CD40 had transient bilateral ocular inflammation (panuveitis) noted 1-week postdose that recovered within 3 weeks postdose. Another animal treated with repeat doses of 30 mg/kg SEA-CD40 was euthanized early (Day 56, approximately 2 weeks post the 3rd dose) due to moribundity caused by a progression of a pre-existing infection with *Plasmodium spp*. The infection was not considered SEA-CD40 related, but the relationship of the progression of the infection was uncertain. The single dose no observed adverse effect level (NOAEL) and highest non-severely toxic dose level (HNSTD) for SEA-CD40 in monkeys were 3 and 30 mg/kg, respectively. The repeat-dose (Q3Wx5) HNSTD for SEA-CD40 in monkeys was 30 mg/kg.

An exploratory single-dose study in human CD40 transgenic mice was performed to compare the pharmacodynamic effects, pharmacokinetics (PK), and injection site toxicity of 1 mcg/kg SEA-CD40 when given via IV or subcutaneous (SC) administration. SEA-CD40 was well tolerated with both routes of administration. No injection site irritation or adverse histopathological findings were observed in the tail, skin, or subcutis with either route of administration. Serum concentration of SEA-CD40 peaked between 2 to 8 hours postdose following IV administration, and at 24 hours postdose following SC administration. SEA-CD40 bioavailability after SC administration was approximately 15%, relative to IV administration. However, differences in area under the concentration-time curve (AUC) exposure did not seem to impact antitumor activity in preclinical models. Consistent with previous studies, IV administration of SEA-CD40 in this mouse model led to increases in cytokine production and B-cell activation and reductions in circulating B cells. While the same pharmacodynamics changes occurred with SC treatment, the responses were attenuated.

A complete summary of the nonclinical data relevant to the SEA-CD40 investigational product and its study in human subjects is provided in the SEA-CD40 IB.

1.7. Pembrolizumab

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

Refer to the IB/approved labeling for detailed background information on MK-3475.

1.7.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley 2005; Hunder 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Okazaki 2001; Greenwald 2005).

The structure of murine PD-1 has been resolved (Zhang 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki 2001; Chemnitz 2004; Sheppard 2004; Riley 2009). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry 2005; Francisco 2010). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in solid tumors.

1.7.2. Preclinical and Clinical Trials with Pembrolizumab

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Strome 2003; Blank 2004; Hirano 2005; Curran 2010; Pilon-Thomas 2010; Weber 2010; Spranger 2014). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome 2003; Zhang 2004; Nomi 2007; Curran 2010; Pilon-Thomas 2010). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo (Curran 2010). Experiments have

confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

1.7.3. Justification for Q3W Pembrolizumab Dose

The planned dose of pembrolizumab for Cohorts 4 and 5 is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and non-small cell lung cancer (NSCLC) indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W) representing an approximate 5 to 7.5 fold exposure range (refer to the IB)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naive, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action (MOA) of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides

similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

1.7.4. Justification for Q6W Pembrolizumab Dose

The planned dose of pembrolizumab for Cohorts 1, 2, and 3 is 400 mg every 6 weeks (Q6W).

A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate (Lala 2018). Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on modeling and simulation (M&S) analyses, given the following rationale:

- PK simulations demonstrating that in terms of pembrolizumab exposures:
    - Average concentration over the dosing interval (C_{avg}) (or area under the curve [AUC]) at 400 mg Q6W is similar to that at the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
    - Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
    - Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab.
    - Exposure-response (E-R) for pembrolizumab has been demonstrated to be flat across indications, and OS predictions in melanoma and NSCLC demonstrate that efficacy at 400 mg Q6W is expected to be similar to that at 200 mg or 2 mg/kg Q3W, given the similar exposures; thus 400 mg Q6W is expected to be efficacious across indications.

1.8. Chemotherapy in NSCLC

Prior to the introduction of immunotherapy, chemotherapy formed the backbone of treatment strategies in NSCLC. While single-agent activity with cisplatin was noted, the benefit over supportive care was marginal with one year survival rates on the order of 10% to 15% (Non-small Cell Lung Cancer Collaborative Group 1995). Gradually, platinum doublet combinations were introduced with significant improvements in one year survival to 33% (Schiller 2002). Given its efficacy and tolerability, platinum doublet therapy with pemetrexed became a standard of care in non-squamous NSCLC until the introduction of immunotherapy (Scagliotti 2008).

1.9. Carboplatin, Pemetrexed, and Pembrolizumab in NSCLC

Carboplatin and pemetrexed preclinical data suggest that, in addition to their cytotoxic function, they possess immune modulatory functions, such as increasing T-cell infiltration and antigen presentation in turn leading to increased T-cell recognition of tumor cells, that have the potential to synergize with immunotherapies like pembrolizumab in NSCLC (Leonetti 2019). KEYNOTE-189 was a global, double-blind, placebo-controlled phase 3 trial comparing platinum-based chemotherapy combined with pemetrexed plus either pembrolizumab or placebo in nonsquamous NSCLC without sensitizing EGFR/ALK anaplastic large-cell lymphoma kinase (ALK) mutations that sought to examine the additional benefit of pembrolizumab when added to platinum doublet chemotherapy. In this trial, there was a significant improvement in OS and progression-free survival (PFS) in the pembrolizumab cohort relative to chemotherapy alone (median OS/PFS of 22 months/9 months vs 10.7 months/4.9 months, respectively); importantly, this relative improvement was noted in all groups regardless of brain or liver metastasis. However, while all levels of tumor proportion score (TPS) had relative benefit, the absolute benefit was not distributed evenly among patients, as patients with TPS ≥50% had a median PFS of 11.1 months compared with 9.2 months and 6.2 months in TPS 1% to 49% and <1% respectively (Gadgeel 2020). Given these differential outcomes dependent on TPS, there is a need to improve outcomes in patients with NSCLC, particularly those with TPS <50%.

1.10. Pembrolizumab Combination Therapy

Pembrolizumab is a highly selective anti-PD-1 humanized mAb that inhibits PD-1 activity by binding to the PD-1 receptor on T cells to block binding to PD-1 ligands (PD-L1 and PD-L2). Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling (Hamid 2013). Anti-PD-(L)1 antibodies, including pembrolizumab, reverse T-cell suppression and induce antitumor responses (Robert 2014). Refer to the current pembrolizumab United States prescribing information for approved treatment indications.

SEA-CD40 and pembrolizumab act through distinct and complementary mechanisms of action. Binding of SEA-CD40 to CD40 on APCs and enhanced crosslinking via FcγRIIIa leads to APC activation and enhanced antigen presentation to tumor specific T cells. It is hypothesized that the activated cytotoxic T cells will migrate into tumor sites, and inhibitory molecules will be blocked by PD-(L)1 mAbs. In preclinical models, SEA-CD40 and the checkpoint inhibitors ipilimumab (anti-CTLA4) or pembrolizumab (anti-PD1) combine to stimulate a T-cell response to common tumor antigen peptides from peripheral blood mononuclear cells (PBMCs) isolated from donors with melanoma (n=3), breast cancer (n=3), or pancreatic cancer (n=3) (Gardai 2015).

The immune checkpoint inhibitors such as pembrolizumab have significant added benefit to patient groups with high unmet need, however, only a subset of patients respond to checkpoint inhibitors, and many patients who initially benefit from checkpoint inhibitors eventually progress. It is hypothesized that by combining checkpoint inhibitors with immune co-stimulatory agents such as SEA-CD40, the antitumor immune response will be more robust, and durable response rates will meaningfully increase. Given that SEA-CD40 is shown to be a biologically and clinically active molecule in heavily pre-treated patients with advanced solid tumors, and pembrolizumab has documented single agent activity in patients with metastatic melanoma and NSCLC, it is hypothesized that pembrolizumab combination therapy could potentially be more

effective than administration of either agent alone. Moreover, both agents are reasonably well tolerated, have few overlapping toxicities, and can be administered in the outpatient setting.

1.11. Chemotherapy Combination Therapy

Although upfront chemoimmunotherapy has improved outcomes significantly in metastatic NSCLC, there is a significant unmet need for improved response rates in patients with TPS <50%, especially in light of the fact that up to half of all NSCLC patients will quickly progress despite treatment and not have the opportunity to receive second-line therapy (Davies 2017). As such, improvement in front-line therapies in patients less responsive to chemoimmunotherapy represents an opportunity to improve survival in these patients by virtue of the ability for them to utilize second-line therapies upon failure. Given that SEA-CD40 appears to have its efficacy enhanced by antigen release from concurrent chemoimmunotherapy administration and that there is an approved chemoimmunotherapy regimen in front-line NSCLC with inferior outcomes in patients with TPS <50%, it is hypothesized that the addition of SEA-CD40 to chemoimmunotherapy in this subset of patients will result in improved outcomes with a manageable safety profile.

There is significant preclinical data in support of combining SEA-CD40 with chemotherapy. Due to its afucosylated Fc backbone, SEA-CD40 appears to engage activating Fc-γ receptors more effectively than other CD40 agonist antibodies (Zeng 2020). Due to this preferential engagement, there is significant augmentation in vitro of immune-activating cytokines, such as CXCL10 and IFN-γ, without commensurate increases in immunosuppressive cytokines, such as IL-10 and MDC, when SEA-CD40 is combined with nab-paclitaxel chemotherapy. Furthermore, when peripheral cytokines are examined in xenograft models, there is an increase in cytokines, as well as tumor-infiltrating CD11b+ macrophages, CD3+ T-cells, and overall T-cells when SEA-CD40 is combined with nab-paclitaxel relative to either therapy alone, indicating that there is synergy between SEA-CD40 and chemotherapy. Compared to other investigational CD40 agonists, there are significantly higher levels of IFN-γ and CXCL10 and lower levels of the immune inhibitory cytokine IL-10 for treated lung cancer cells when SEA-CD40 is combined in vitro with oxaliplatin, a chemotherapy known to induce immunogenic cell death (ICD), indicating immunologic synergy (Sun 2019). Notably, SEA-CD40 and oxaliplatin combined induced significant increases in IL-12p40 and CXCL10 in mice bearing solid tumors, indicating that this synergy between ICD-inducing chemotherapy and SEA-CD40 holds in vivo. Given that carboplatin and pemetrexed are both chemotherapies known to induce ICD when utilized alone or in combination with other chemotherapies and that SEA-CD40 appears to synergize specifically with ICD-inducing chemotherapy, it is believed that the combination of standard-of-care chemotherapy with SEA-CD40 will provide significant therapeutic benefit in front-line metastatic NSCLC (Novosiadly 2018; Schaer 2019; Flieswasser 2020).

1.12. Summary of Clinical Study SGNS40-001

An ongoing phase 1 dose-regimen finding study, SGNS40-001, is evaluating the safety, tolerability, and antitumor activity of SEA-CD40 as monotherapy in subjects with advanced solid and hematologic malignancies. SGNS40-001 is also evaluating SEA-CD40 in combination with chemotherapies and/or pembrolizumab in subjects with advanced solid tumors (eg, melanoma, NSCLC, head and neck squamous cell carcinoma [HNSCC], and pancreatic cancer).

In monotherapy, SEA-CD40 was administered either IV or SC on Day 1 of each 3-week cycle at doses ranging from 0.6 mcg/kg to 3 mg/kg. In combination therapy, SEA-CD40 was administered IV on Day 1 and pembrolizumab 200 mg is administered on Day 2 of each 21-day cycle. Subjects with pancreatic cancer were administered gemcitabine and nab-paclitaxel on Days 1, 8, and 15 of each 28-day cycle; SEA-CD40 on Day 3 of each 28-day cycle; and pembrolizumab 400 mg Q6W. Subjects continued on study treatment until disease progression or unacceptable toxicity.

The maximum tolerated dose (MTD) for SEA-CD40 monotherapy was not exceeded for subjects with solid tumors or lymphomas. As detailed in the SEA-CD40 IB, infusion or hypersensitivity reactions (IHRs) are an identified risk for SEA-CD40 and have been observed in subjects administered SEA-CD40 in Study SGNS40-001. The combination of SEA-CD40 and pembrolizumab was determined to be tolerable in Study SGNS40-001.

A summary of clinical safety data from Study SGNS40-001 is provided in the SEA-CD40 IB.

1.13. Rationale for Study

Based on prior experience with dacetuzumab and SEA-CD40 (Section 1.12) and the potential role of CD40 in antitumor immunity, SEA-CD40 may have broad therapeutic potential in many types of malignancies. By comparing outcomes in subjects receiving SEA-CD40 combination therapy to those of historical controls, we will determine the potential for SEA-CD40 when combined with approved therapies. Efficacy data acquired through this trial will inform decisions to pursue larger randomized trials for individual indications. Initially, the trial will focus on populations that are most likely to have a measurable benefit within the confines of a smaller sample size, specifically melanoma and NSCLC with TPS <50%.

1.14. Assessment of Benefit-Risk

This basket study will enroll subjects with multiple tumor types to evaluate whether the addition of SEA-CD40 to standard of care treatments can improve response rates and/or survival. Preliminary safety data from the ongoing phase 1 study (SGNS40-001; summarized in Section 1.12) suggest that SEA-CD40 combined with pembrolizumab and/or chemotherapy is tolerable. A summary of clinical safety data from Study SGNS40-001 is provided in the SEA-CD40 IB.

Initially, enrollment in this study will be limited to subjects with NSCLC and melanoma; the histologies included may be expanded via protocol amendment. SEA-CD40 is believed to have the potential to synergize with current chemoimmunotherapy strategies and could provide clinical benefit within patient populations in which immunotherapy is standard of care, especially those with suboptimal responses to therapy. Given that SEA-CD40 combined with chemotherapy and immunotherapy has demonstrated tolerability in the phase 1 study (SGNS40-001) and that preclinical data support these combinations, the chosen patient populations are considered appropriate for inclusion in this trial.

The sponsor has conducted a risk assessment for the concomitant use of COVID-19 vaccines. It has determined that the administration of a COVID-19 vaccine during this trial is considered a concomitant medication that does not require advice or timing of the vaccine beyond the guidance already outlined in this study protocol (see Section 5.4.2). This patient population is at

risk for severe COVID-19 disease and therefore will benefit from administration of a vaccine that prevents severe disease.

2. OBJECTIVES

This study will evaluate the antitumor activity, safety, and tolerability of SEA-CD40 in subjects with advanced or metastatic solid malignancies. Specific objectives and corresponding endpoints for the study are summarized below:

Primary Objective	Corresponding Primary Endpoint
• To evaluate the antitumor activity of SEA-CD40 combined with other therapies	• Confirmed Objective Response Rate (ORR; confirmed complete response [CR] or partial response [PR]) according to RECIST v1.1 per investigator assessment (Eisenhauer 2009)
Secondary Objectives	**Corresponding Secondary Endpoints**
• To evaluate the safety and tolerability of SEA-CD40 combined with other therapies	• Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) • Type, incidence, and severity of laboratory abnormalities • Frequency of treatment interruptions, dose reductions, and treatment discontinuations due to AEs
• To evaluate control of disease	• Disease control rate (DCR; confirmed CR, PR, and stable disease [SD]) per investigator assessment
• To evaluate durability of response in subjects who respond to study drug(s)	• Duration of response (DOR; duration of confirmed CR or PR) per investigator assessment
• To evaluate PFS and survival	• Progression-free survival (PFS) per investigator assessment • Overall survival (OS)
Exploratory Objectives	**Corresponding Exploratory Endpoints**
• To characterize the pharmacokinetics (PK) of SEA-CD40 and incidence of antidrug antibodies (ADAs) when SEA-CD40 is administered in combination with other therapies	• Estimates of selected PK parameters • Incidence of ADAs

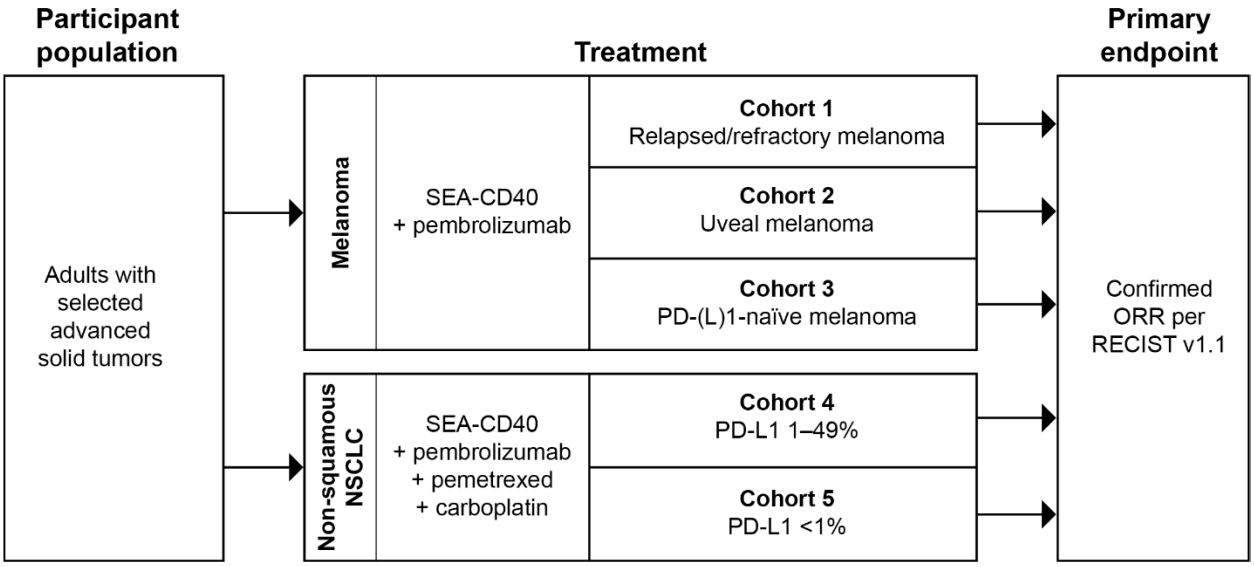
Cohorts 1, 2, and 3 (Melanoma): • To evaluate selected pharmacodynamic parameters of interest for SEA-CD40.	*Cohorts 1, 2, and 3 (Melanoma):* • Exploratory correlations between QTc and plasma concentrations of SEA-CD40
To assess exploratory biomarkers of response, toxicity, and resistance of SEA-CD40 in combination with other therapies	Actual and change from baseline values in immune subsets and cytokines in peripheral blood
• To evaluate the antitumor activity of SEA-CD40 combined with other therapies per Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST)	• Confirmed ORR (immune complete response [iCR] or immune partial response [iPR]) according to iRECIST
• To evaluate patient-reported outcomes of disease/treatment-related symptoms, health-related quality of life (HRQoL), and function	*All Cohorts:* • Actual and change from baseline scores on the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) *Cohorts 4 and 5 only (NSCLC):* • Time-to-deterioration (TTD) in either cough, dyspnea, or chest pain (whichever deteriorates first) as measured by the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) • Actual and change from baseline values in NSCLC-SAQ domains and total scores

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a phase 2, global, open-label, multicenter trial designed to assess the activity, safety, and tolerability of SEA-CD40 in combination with standard-of-care therapies in adults with selected solid tumors. The study will include multiple indication-specific cohorts. Up to approximately 200 subjects may be enrolled in this study. Figure 1 presents the overall study design.

Figure 1: Study Design



For the NSCLC cohorts (Cohorts 4 and 5), the safety monitoring committee (SMC) will assess safety after the first 6 subjects have completed at least 1 treatment cycle. For all cohorts, an interim analysis will be performed after at least 15 subjects have received the study drugs and are response evaluable in each cohort. While the interim analysis is performed, enrollment in the cohort may continue. The Bayesian predictive probability approach will be used to inform decision-making for continued enrollment (Lee 2008b). At the time of the interim analysis, the predictive probability of success (PpoS) will be calculated. Based on the totality of activity and safety data, together with the PpoS, the cohort may continue or be stopped early by the sponsor. A cohort may also be discontinued at any point at the discretion of the sponsor.

On a periodic basis, an SMC will monitor the safety of subjects in the study (Section 3.1.7). Ongoing, real-time review of subject safety will also be conducted by the sponsor's drug safety department throughout the study.

Response will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) scans Q6W from the first dose of study drug for 24 weeks and every 12 weeks thereafter until disease progression, initiation of new anticancer treatment, study termination by the sponsor, or death, whichever occurs first. The determination of antitumor activity will be based on objective response rate (ORR) assessments as defined by RECIST v1.1 and by immune-related Response Evaluation Criteria in Solid Tumors (iRECIST). Treatment decisions will be determined by the investigator.

3.1.1. Cohorts 1, 2, and 3 (Melanoma)

Cohorts 1, 2, and 3 will evaluate SEA-CD40 in combination with pembrolizumab in subjects with unresectable melanoma. Cohort 1 will enroll subjects with relapsed and/or refractory melanoma who have received up to 3 prior lines of systemic therapy and have progressed on treatment with an anti-PD-(L)1 mAb as the most recent therapy. Cohort 2 will enroll subjects with metastatic uveal melanoma. Cohort 3 will enroll subjects with metastatic PD-(L)1-naive melanoma. Full eligibility criteria are detailed in Section 4. Due to differences in standard of care, subjects in France will not be enrolled in Cohort 1.

Initially, up to 15 subjects may enroll in each cohort. Interim safety and efficacy analyses will be performed for each cohort after 15 subjects have received study drug and are response evaluable. Cohorts may continue to enroll up to an additional 25 subjects, for a total of up to approximately 40 subjects in each cohort.

3.1.2. Cohorts 4 and 5 (NSCLC)

Cohorts 4 and 5 will evaluate SEA-CD40 in combination with carboplatin, pemetrexed, and pembrolizumab in subjects with stage IV non-squamous NSCLC. Cohort 4 will enroll subjects with PD-L1 TPS expression of 1%–49%. Cohort 5 will enroll subjects with PD-L1 TPS expression <1%.

Initially, 6 total subjects will be enrolled across Cohorts 4 and 5; safety will be assessed after the first treatment cycle. If approved by the SMC, Cohorts 4 and 5 may continue to enroll up to 15 subjects per cohort. Interim safety and efficacy analyses will be performed for each cohort after 15 subjects have received study drug and are response evaluable. Cohorts may continue to enroll up to an additional 25 subjects, for a total of up to approximately 40 subjects in each cohort.

3.1.3. Duration of Treatment

Subjects who achieve stable disease (SD) or better may continue study treatment for approximately 2 years or until unacceptable toxicity, confirmed disease progression, withdrawal of consent, or study termination, whichever occurs first.

Pembrolizumab administration will be discontinued once the subject has completed approximately 2 years with pembrolizumab (35 administrations for Q3W dosing or 18 administrations for Q6W dosing).

Subjects with progressive disease (PD) per RECIST v1.1 should have follow-up imaging no later than 6 to 8 weeks beyond the initial diagnosis of radiographic disease progression to confirm progressive disease per iRECIST.

Subjects with unconfirmed progressive disease (iUPD) per iRECIST may continue study treatment at the discretion of the investigator, with additional consent, if all of the following criteria are met:

- Evidence of clinical benefit, defined as the stabilization or improvement of disease related symptoms, as assessed by the investigator
- No symptoms or signs (including worsening laboratory values) indicating unequivocal disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status that can be attributed to disease progression
- No tumor growth at critical anatomical sites (eg, leptomeningeal disease) that cannot be managed and stabilized by protocol-allowed medical interventions prior to repeat dosing

3.1.4. Stopping Criteria

3.1.4.1. Enrollment Pause at the Cohort Level

If a death is considered to be related to SEA-CD40 by the sponsor, enrollment will be paused until:

1. The case is reviewed by the investigator, the sponsor, and the SMC, and
2. The sponsor has notified applicable regulatory authorities of the outcome of the safety assessment and justification for restarting enrollment in the affected cohorts, and has received approval to resume, if required by local regulations.

3.1.4.2. Enrollment Halt for the Entire Study

Enrollment in the entire study will be halted by the sponsor if the overall benefit-risk balance is considered negative.

Safety will be continuously monitored throughout the study by the sponsor and the SMC, with consideration for enrollment halt if the incidence and/or the severity of toxicity leads to a risk-benefit assessment that is unacceptable to the study population. The sponsor will consult with the SMC to consider whether to allow subjects already receiving treatment to continue, to consider modifications to the protocol to continue enrollment, or to terminate the study.

If enrollment is halted due to safety concerns, enrollment can only be restarted after appropriate amendments and notifications to Regulatory Authorities, with approval to resume, if required by local regulations.

3.1.5. End of Study

The study will be closed 3 years after the last subject receives the last dose, or when no subjects remain in follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.3.2).

If the sponsor terminates the study early, investigators are instructed to continue disease assessments per protocol, unless otherwise indicated by the sponsor, until the study termination date. Subjects discontinuing treatment will be followed for 30 days post-treatment for SEA-CD40 and/or chemotherapy and 90 days post-treatment for pembrolizumab, unless safety concerns warrant further follow-up. Patients in survival follow-up at the time of early study termination will be contacted one last time, regardless of the date of the prior assessment, for final survival assessment. The investigator will be expected to monitor for and report any serious adverse events (SAEs) and pregnancies, as detailed in Section 7.7.1.3 and Section 7.7.6. Truncated data may be collected at the discretion of the sponsor.

3.1.6. Retreatment

Retreatment is not permitted on this study.

3.1.7. Safety Monitoring Committee

The SMC will monitor safety throughout the study and will make recommendations to the sponsor. The SMC is composed of site investigators and representatives from the sponsor

(including the study medical monitor, drug safety representative, and biostatistician). The SMC will review clinical data from enrolled subjects for safety assessment. The committee will monitor the safety of subjects in this study through regular and/or ad hoc meetings that include review of data pertaining to treatment-emergent toxicities. Further details will be documented in an SMC charter.

3.1.8. Trial Operations and Data Collection after SEA-CD40 Expiry

If at least 6 months have elapsed since the last subject was enrolled in the study, and if there are no more than 15 subjects still on study receiving only drug(s) with a known safety profile (such as pembrolizumab/pemetrexed combination therapy or pembrolizumab monotherapy), a database lock of the study may occur to allow the analysis of the SEA-CD40-related study data.

Any remaining subjects may continue to receive study treatments other than SEA-CD40 (pembrolizumab with or without carboplatin and pemetrexed) per protocol and be seen by the investigator per usual standard of care. Chemotherapies may be supplied per Section 5.1.3.2. The investigator will be expected to monitor for progression and report any SAEs and pregnancies, as outlined in Section 7.7.1.3 and Section 7.7.6. No other data will be collected. The remaining subjects are considered to be on study until a discontinuation criterion is met, or the study is terminated by the sponsor.

3.2. Discussion and Rationale for Study Design

This study will evaluate SEA-CD40 in combination with standard of care treatments for advanced solid tumor cancers.

3.2.1. Rationale for Study Design

This is a phase 2 study designed to assess the efficacy and safety of SEA-CD40 combination therapy. By comparing subjects on study to relevant historical controls, we hope to demonstrate the utility of SEA-CD40 in treating solid tumors. Given its immunologic mechanisms of action, SEA-CD40 has potential efficacy across a broad range of tumor types when administered in combination with agents targeting PD-(L)1 inhibition and/or chemotherapy. Efficacy will be assessed by ORR as the primary endpoint. Additional cohorts of interest may be added to this study via a protocol amendment.

Cohorts 1, 2, and 3 will assess SEA-CD40 in combination with pembrolizumab. This combination was previously determined to be tolerable in Study SGNS40-001 (see Section 1.12, and the SEA-CD40 IB). Cohorts 4 and 5 will assess SEA-CD40 in combination with carboplatin, pemetrexed, and pembrolizumab. Safety of this combination will be reviewed by the SMC after 6 subjects across Cohorts 4 and 5 have received at least 1 cycle of treatment. If after this safety review the combination is deemed tolerable, enrollment in Cohorts 4 and/or 5 may continue.

In all Cohorts, an interim analysis of safety and efficacy will be performed after 15 subjects are response evaluable. Based on the totality of data, an additional 25 subjects (for a total of 40 subjects per cohort) may be enrolled to allow for appropriate power to detect a difference between the treatment group and relevant historical controls.

3.2.2. Method of Assigning Subjects to Treatment Groups

Subjects will be enrolled in cohorts based on tumor type and according to the eligibility criteria detailed in Section 4. For Cohorts 4 and 5, subjects with NSCLC will be enrolled based upon level of PD-L1 expression by local assessment.

3.2.3. Rationale for Selection of SEA-CD40 Dose and Schedule

SEA-CD40 will be administered at a dose of 10 mcg/kg every 21 days (Q21d).

In the phase 1 study, SGNS40-001, this dose and schedule, administered as monotherapy and in combination with pembrolizumab and/or chemotherapy (gemcitabine and nab-paclitaxel) was adequately tolerated and demonstrated an acceptable safety profile, potent pharmacodynamic activity, and preliminary evidence of clinical activity. More information is provided in the SEA-CD40 IB.

In preclinical models, optimal synergy has been reported when CD40 agonists are administered approximately 2 days after chemotherapy (Nowak 2003; Winograd 2015; Byrne 2016a; Byrne 2016b; Morrison 2020). This timing is hypothesized to coincide with antigen release from chemotherapy, which may facilitate a synergistic immune response. Comparable timing has been utilized in prior clinical trials of CD40 agonists (Beatty 2013; Vonderheide 2013a; Vonderheide 2013b; Coveler 2020; O'Hara 2021).

Synergy between SEA-CD40 and PD-(L)1 targeting therapy is enhanced when these agents are administered on separate days (Gardai 2017) (Seagen, data on file). Thus, SEA-CD40 and pembrolizumab will be dosed on separate days.

3.2.4. Blinding and Unblinding

This is an open-label study.

4. STUDY POPULATION

Subjects must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and subjects are to be reviewed in the event of a good clinical practice audit and/or health regulatory authority inspection.

4.1. Inclusion Criteria

1. Histologically or cytologically confirmed diagnosis of unresectable malignancy of one of the following types:
    a. Cohort 1: Relapsed and/or refractory metastatic melanoma
        i. Uveal/ocular melanoma is excluded.
        ii. Subjects may have received up to 3 prior lines of systemic therapy for advanced disease (prior adjuvant/neoadjuvant immunotherapy such as interferon, anti-PD-(L)-1, or anti-CTLA-4 will not count as a line of therapy as long as relapse did not occur during treatment or within 6 months of treatment discontinuation).

iii. Subjects must have progressed on treatment with an anti-PD-(L)1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. PD-(L)1 treatment progression is defined as meeting all of the following criteria:

- Has received at least 2 doses of an approved anti-PD-(L)1 mAb.
- Has demonstrated disease progression after PD-(L)1 as defined by RECIST v1.1. The initial evidence of PD is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression.
- Progressive disease has been documented within 12 weeks from the last dose of anti-PD-(L)1 mAb.
    - Progressive disease is determined according to iRECIST.
    - This determination is made by the investigator. Once PD is confirmed, the initial date of PD documentation will be considered the date of disease progression.
- Last dose of anti-PD-(L)1 must have been within 90 days prior to enrollment; most recent anti-PD-(L)1 therapy must not have been discontinued due to Grade 3 or higher immune-related adverse event (irAE).

iv. Subjects entered in the study after completion of enrollment for the interim analysis (see Section 9.3.10) should have a tumor site accessible for biopsy and agree to have fresh baseline and on-treatment biopsies, if appropriate in the opinion of the investigator. An archival sample collected within 30 days prior to the first dose of study drug may substitute for the baseline biopsy.

v. Subjects with a targetable BRAF mutation must have been treated with, been intolerant of, or declined treatment with BRAF/MEK targeted therapy prior to study entry.

vi. Due to differences in standard of care, subjects in France will not be enrolled in Cohort 1.

b. Cohort 2: Metastatic uveal melanoma

i. Subjects must not have received prior treatment for advanced or metastatic disease except as follows:

- Prior adjuvant/neoadjuvant immunotherapy such as interferon, anti-PD-(L)1, or anti-CTLA-4 if relapse did not occur during treatment or within 6 months of treatment discontinuation

ii. No prior regional, liver-directed therapy including chemotherapy, radiotherapy, or embolization

iii. Subjects entered in the study after completion of enrollment for the interim analysis (see Section 9.3.10) should have a tumor site accessible for biopsy and agree to have fresh baseline and on-treatment biopsies, if appropriate in the

opinion of the investigator. An archival sample collected within 30 days prior to the first dose of study drug may substitute for the baseline biopsy.

c. Cohort 3: Metastatic PD-(L)1-naive melanoma

   i. Uveal/ocular melanoma is excluded

   ii. Subjects must not have received prior treatment for advanced or metastatic disease except as follows:

   - Prior adjuvant/neoadjuvant immunotherapy such as interferon, anti-PD-(L)1, or anti-CTLA-4 if relapse did not occur during treatment or within 6 months of treatment discontinuation
   - For subjects with a targetable BRAF mutation, prior BRAF/MEK targeted therapy is allowed if completed 4 weeks prior to first dose of study treatment
   - Subjects with a targetable BRAF mutation who are rapidly progressing should be treated with BRAF/MEK targeted therapy to stabilize disease prior to enrollment, unless contraindicated

d. Cohorts 4 and 5: Non-squamous NSCLC

   i. Subjects must have stage IV disease per American Joint Committee on Cancer (AJCC) 8th edition

   ii. No known driver mutations/alterations mutation for which targeted therapy is available (eg, EGFR, ALK, etc.)

   iii. Must have non-squamous histology. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the subject is ineligible

   iv. No prior therapy for metastatic disease. Adjuvant/neoadjuvant therapy is allowed for non-metastatic disease if fully completed at least 12 months prior to diagnosis of metastatic disease.

   v. No prior treatment with anti-PD-(L)1 or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms

   vi. Able and willing to take folic acid or vitamin B12 supplementation

   vii. Does not have symptomatic ascites or pleural effusion. Subjects who are clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) are eligible

   viii. Has not received radiation therapy to the lung >30 Gy within 6 months prior to first dose of study drug

   ix. **Cohort 4**: PD-L1 1%–49% TPS by local assessment

   x. **Cohorts 5**: PD-L1<1% TPS by local assessment

2. Have provided archival tumor tissue from locations not radiated prior to biopsy; formalin fixed specimens after the subject has been diagnosed with metastatic disease will be

preferred. Biopsies obtained prior to receipt of adjuvant/neoadjuvant chemotherapy will be permitted if recent biopsy is not feasible. If archival tumor sample is not available, a fresh baseline biopsy is required.

3. Age 18 years or older.
4. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1 (see Appendix A for conversion of performance status using Karnofsky scale, if applicable).
5. Measurable disease per RECIST v1.1 at baseline.
   - Lesions that have had prior intralesional therapies including T-VEC are not considered measurable
   - Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions
6. The following baseline laboratory data:
   - **Cohorts 1, 2, and 3:** absolute neutrophil count (ANC) ≥1500/μL

     Cohorts 4 and 5: ANC ≥2000 μL.
   - Hemoglobin (Hgb) ≥9 g/dL without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Subjects can be on stable dose of erythropoietin (≥ approximately 3 months).
   - Platelet count ≥100,000/μL
   - Serum bilirubin ≤1.5 x upper limit of normal (ULN) or ≤3 x ULN for subjects with Gilbert's disease or documented hepatic tumor involvement
   - Creatinine clearance (CrCl) ≥45 mL/min calculated per institutional standard
   - ALT and aspartate aminotransferase (AST) ≤2.5 x ULN (≤5 x ULN if there is evidence of hepatic involvement by malignant disease)
7. Subjects of childbearing potential, as defined in Section 4.3, under the following conditions:
   a. Must have a negative serum or urine pregnancy test (minimum sensitivity 25 mIU/mL or equivalent units of beta human chorionic gonadotropin [β-hCG]) result within 3 days prior to the first dose of any study drug. Subjects with false positive results and documented verification that the subject is not pregnant are eligible for participation
   b. Cohorts 1, 2, and 3:
      i. Must agree not to try to become pregnant during the study and for at least 120 days after the final dose of study drug
      ii. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 120 days after the final dose of study drug

iii. If sexually active in a way that could lead to pregnancy, must consistently use the acceptable combinations of contraceptive methods (as defined in Appendix B) starting at time of informed consent and continuing throughout the study and for at least 120 days after the final dose of study drug

c. Cohorts 4 and 5:

i. Must agree not to try to become pregnant during the study and for at least 6 months after the final dose of study drug

ii. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 6 months after the final dose of study drug

iii. If sexually active in a way that could lead to pregnancy, must consistently use the acceptable combinations of contraceptive methods (as defined in Appendix B) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug

8. Subjects born male, under the following conditions:

a. Cohorts 1, 2, and 3:

i. Must agree not to donate sperm starting at time of informed consent and continuing until the final dose of study drug.

ii. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use the acceptable combinations of contraceptive methods (as defined in Appendix B) starting at time of informed consent and continuing until the final dose of study drug.

iii. If sexually active with a person who is pregnant or breastfeeding, must consistently use a condom (as defined in Appendix B) starting at time of informed consent and continuing until the final dose of study drug.

b. Cohorts 4 and 5:

i. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 6 months after the final dose of study drug.

ii. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use the acceptable combinations of contraceptive methods (as defined in Appendix B) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug

iii. If sexually active with a person who is pregnant or breastfeeding, must consistently use a condom (as defined in Appendix B) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug.

9. The subject must provide written informed consent.

4.2. Exclusion Criteria

1. History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS ≥90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.
2. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
3. Previous exposure to CD40-targeted therapy.
4. Currently on chronic systemic steroids. Physiologic corticosteroid replacement therapy (eg, prednisone 10 mg equivalent or less per day) or intermittent use of bronchodilators, inhaled steroids, topical steroids, or local steroid injections is allowed.
5. Has had an allogeneic tissue/solid organ transplant.
6. Any uncontrolled Grade 3 or higher (per the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], v 5.0) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study drug. Routine antimicrobial prophylaxis is permitted.
7. Known to be positive for hepatitis B by surface antigen expression. Known to have active hepatitis C infection (positive by polymerase chain reaction [PCR] or on antiviral therapy for hepatitis C within the last 6 months). Subjects who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
8. Note: No testing for hepatitis B and hepatitis C is required unless mandated by a local health authority.
9. Known to be positive for human immunodeficiency virus (HIV). Note: No HIV testing is required unless mandated by local health authority.
10. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV (see Appendix C) within 6 months prior to their first dose of study drug.
11. Congestive heart failure, Class III or IV, by the New York Heart Association criteria.
12. Current therapy with other systemic anti-neoplastic or investigational agents.
13. Radiotherapy within 2 weeks prior to first dose of study drug. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

14. Major surgery and/or any complications from the surgery from which the subject has not recovered adequately.
15. *This criterion has been removed (see Inclusion Criterion 7).*
16. Known hypersensitivity to any excipient contained in the drug formulation of SEA-CD40 or other study drugs.
17. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). 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 allowed.
18. Has a diagnosis of clinically significant immunodeficiency.
19. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease. Lymphangitic spread of malignancy is not exclusionary.
20. Has received a live or live-attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Administration of killed vaccines are allowed.
21. Estimated life expectancy <12 weeks.
22. Other serious underlying medical condition that, in the opinion of the investigator, would impair the subject's ability to receive or tolerate the planned treatment and follow-up.
23. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study.
24. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to treatment.
25. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

    Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
26. **Cohorts 4 and 5**: Subjects with CrCl <80 mL/min who have had treatment with ibuprofen or other nonsteroidal anti-inflammatory drugs (NSAIDs) during the 2 days before pemetrexed administration.
27. **Cohorts 4 and 5**: Subjects who have received long acting NSAIDs (such as piroxicam or rofecoxib) during the 5 days prior to pemetrexed administration.

4.3. Reproductive Potential

A person of childbearing potential is anyone who has experienced menarche and who has not undergone permanent sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months

of amenorrhea in a person over 45 years old in the absence of other biological, physiological, or pharmacological causes.

A subject who can get someone pregnant is anyone who has testes and who has not undergone permanent sterilization (defined as bilateral orchidectomy).

4.4. Removal of Subjects from Study Treatment or Assessments

Seagen or their designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and case report form (CRF).

4.4.1. Discontinuation of Study Treatment

A subject's study treatment may be discontinued for any of the following reasons:

- PD
- Adverse event (AE)
- Pregnancy
- Investigator decision
- Subject decision, non-AE
- Study termination by sponsor
- Other, non-AE

Subjects who discontinue from study treatment will remain on study for follow-up unless they withdraw consent.

Study treatment will be considered to be ongoing if a subject is receiving any study drug. If a study drug is discontinued, study treatment may continue with the remaining drug(s).

Subjects must discontinue pembrolizumab after completion of 18 administrations for Q6W dosing or 35 administrations for Q3W dosing (approximately 2 years). Note: The number of administrations is calculated starting with the first dose of pembrolizumab.

4.4.2. Subject Withdrawal from Study

Any subject may be discontinued from the study for any of the following reasons:

- Subject withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

5. TREATMENTS

5.1. Treatments Administered

All subjects will receive SEA-CD40, the investigational agent under study in this protocol.

All study treatments are outlined in Table 6 and in Sections 5.1.1, 5.1.2, and 5.1.3.

Table 6: Study Treatments

Study Drug	Route of Administration	Dose/Potency		Frequency	Schedule
SEA-CD40 (all cohorts)	IV infusion	10 mcg/kg		Q21d	**Cohorts 1, 2, and 3:** Day 1 and Day 22 of 42-day cycles
					Cohorts 4 and 5: Day 3 of 21-day cycles
Pembrolizumab (all cohorts)	IV infusion	**Cohorts 1, 2, and 3:**	400 mg	Q42d (Q6W dosing)	Day 8 of 42-day cycles
		Cohorts 4 and 5:	200 mg	Q21d (Q3W dosing)	Day 1 of 21-day cycles
Pemetrexed (Cohorts 4 and 5 only)	IV infusion	500 mg/m^2		Q21d	Day 1 of 21-day cycles
Carboplatin (Cohorts 4 and 5 only)	IV infusion	AUC 5 mg/mL/min		Q21d	Day 1 of 21-day Cycles 1–4

If any study treatment is eliminated from a cycle, treatment should be resumed on the same schedule when clinically appropriate.

For Cohorts 4 and 5, on days when both pembrolizumab and chemotherapy are administered, the order of administration should be

1. Pembrolizumab infusion
2. Chemotherapy pre-medications
3. Pemetrexed
4. Carboplatin

5.1.1. SEA-CD40

The preparation, administration, and storage of SEA-CD40 is detailed in the Pharmacy Instructions.

5.1.1.1. Description

SEA-CD40 is a sterile, preservative-free, colorless to slightly yellow, clear to slightly opalescent solution for administration. SEA-CD40 drug product consists of SEA-CD40 (10 mg/mL),

trehalose, histidine, and polysorbate 20. The pH of the product is approximately 5.5. SEA-CD40 is supplied by Seagen in single-dose glass vials. SEA-CD40 drug product is labeled with a nominal content of 100 mg/vial. Each vial contains 105 mg of SEA-CD40, which allows the label quantity to be withdrawn for use.

5.1.1.2. Dose and Administration

SEA-CD40 will be administered by IV infusion Q21d at a dose of 10 mcg/kg

SEA-CD40 requires dilution prior to administration.

Initially, SEA-CD40 is administered via IV infusion at a fixed infusion rate not to exceed 10 mcg/min. The minimum allowable duration of infusion should be calculated in the following manner:

Total Dose (mcg) ÷ 10 mcg/min = Infusion Duration (minutes)

If the initial infusion at a rate of 10 mcg/min is adequately tolerated with no infusion-related reaction (IRR) ≥ Grade 1, for the second dose (per investigator discretion), SEA-CD40 may be administered more rapidly but should be administered no faster than **15 mcg/min**.

If the infusion remains adequately tolerated with the increased rate with no IRR ≥ Grade 1, for subsequent doses (per investigator discretion), SEA-CD40 may be administered more rapidly but should be administered no faster than **20 mcg/min**. However, given the variability of infusion pumps from site to site, a window between –5 minutes and +10 minutes is permitted (eg, if the infusion time is 30 minutes [–5 min/+10 min]).

See the Pharmacy Instructions for details.

IRRs related to SEA-CD40 have been observed. To reduce the risk of IRRs with SEA-CD40, subjects will receive premedication/postmedication as described in Section 5.3. Additionally, after completion of the first infusion of SEA-CD40, subjects will be observed for at least 2 hours for potential IRRs and must have stable vital signs prior to discharge from clinic. Subsequent infusions will not require this observation period unless indicated by the investigator.

5.1.1.3. Storage and Handling

The controlled location for storage of vials and solutions containing SEA-CD40 must be accessible only to the pharmacist, the investigator, or a duly designated person. SEA-CD40 does not contain preservatives; therefore, opened and reconstituted vials should be used immediately. Information on storage and handling of reconstituted product is provided in the Pharmacy Instructions. It is recommended that SEA-CD40 vials and solutions be stored protected from direct sunlight until the time of use. Reconstituted vials must not be shaken.

Drug accountability procedures are provided in the Pharmacy Binder.

5.1.1.4. Packaging and Labeling

SEA-CD40 is supplied in a clear glass, single-dose vial. The vials will be labeled as containing SEA-CD40.

5.1.1.5. Preparation

Detailed drug preparation instructions are provided in the Pharmacy Instructions.

5.1.2. Pembrolizumab

5.1.2.1. Description

Pembrolizumab is a humanized mAb that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa Ig with an approximate molecular weight of 149 kDa.

Pembrolizumab is supplied as a 100 mg/4 mL (25 mg/mL) solution in a single-use vial.

Pembrolizumab for injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine, polysorbate 80, sucrose, L-methionine and Water for Injection, United States Pharmacopeia (USP).

5.1.2.2. Method of Procurement

Pembrolizumab will be provided to all study sites by the sponsor. Pembrolizumab will be relabeled by the sponsor to meet country-specific regulatory requirements.

5.1.2.3. Dose and Administration

Cohorts 1, 2, and 3 (Melanoma)

Pembrolizumab will be administered using IV infusion on Day 8 of each 42-day treatment cycle. Pembrolizumab will be administered as a dose of 400 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between –5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes [–5 min/+10 min]).

Pembrolizumab will be discontinued after 18 administrations Q6W (approximately 2 years; see Section 4.4.1).

Cohorts 4 and 5 (NSCLC)

Pembrolizumab will be administered on Day 1 of each 21-day treatment cycle. Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between –5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes (–5 min/+10 min).

Pembrolizumab will be discontinued after 35 administrations Q3W (approximately 2 years; see Section 4.4.1).

5.1.2.4. Storage and Handling

Pembrolizumab should be stored and handled per the pembrolizumab Pharmacy Manual.

5.1.2.5. Preparation

The pembrolizumab Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

5.1.3. Pemetrexed and Carboplatin

Pemetrexed and carboplatin will be administered to subjects in Cohorts 4 and 5 (NSCLC) only.

5.1.3.1. Description

Pemetrexed

Pemetrexed is a pyrimidine-based folate antimetabolite that inhibits the enzymes involved in purine and pyrimidine nucleotide synthesis (thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide formyl transferase). Notably, this multienzyme inhibition is unique to pemetrexed as other antimetabolites, such as methotrexate and 5-flurouracil, only inhibit single enzymes. Through inhibition of nucleotide synthesis, DNA and RNA production is limited, reducing cell growth throughout the body.

Carboplatin

Carboplatin is a cisplatin analog that replaces the chloride atoms with a carboxycyclobutane moiety, reducing its toxicity profile. The drug is cell cycle non-specific, producing DNA crosslinks between DNA strands, thus inhibiting DNA synthesis and cancer cell growth.

5.1.3.2. Method of Procurement

In the US and Canada, pemetrexed and carboplatin will be sourced by study sites from commercial supply. In other countries, pemetrexed and carboplatin may be provided to study sites by the sponsor or investigational sites may use locally available marketed products authorized for use in their respective country.

5.1.3.3. Dose and Administration

Administer **pemetrexed** at a dose of 500 mg/m^2.

Administer **carboplatin** at a dose of AUC 5 (using Calvert formula). Carboplatin dose is not to exceed 750 mg. CrCl should be calculated using the Cockcroft-Gault equation.

- Calvert Formula: Total Dose (mg) = (target AUC) x (CrCl + 25)

The CrCl used in the Calvert formula should not exceed 125 mL/min.

- Maximum carboplatin dose (mg) = target AUC 5 (mg•min/mL) x (125 + 25) = 5 x 150 mL/min = 750 mg

5.1.3.4. Storage and Handling

Pemetrexed and carboplatin should be stored and handled per their respective United States Prescribing Information (USPI) or local labels.

5.1.3.5. Packaging and Labeling

Refer to the pemetrexed and carboplatin package inserts for packaging and labeling information. Outside of the US, pemetrexed and carboplatin will be relabeled by the sponsor.

5.1.3.6. Preparation

Pemetrexed and carboplatin should be prepared per their respective USPIs or local labels.

5.2. Dose Modifications

5.2.1. Dose Modifications and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab and/or SEA-CD40

AEs associated with pembrolizumab combination exposure, including coadministration with additional compounds, may represent an immune-related etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and/or SEA-CD40 and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab and/or SEA-CD40 are provided in Table 9.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab or SEA-CD40, the investigator does not need to follow the treatment guidance.

Attribution of Toxicity

When study 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 SEA-CD40 alone, or to pembrolizumab alone, for AEs listed in Table 7, SEA-CD40 and pembrolizumab must be held according to the criteria in Table 7.

Holding Study Drugs

When study drugs are administered in combination, if the AE is considered immune-related, both SEA-CD40 and pembrolizumab should be held according to recommended dose modifications.

Table 7: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab and/or SEA-CD40

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab and/or SEA-CD40 must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab/SEA-CD40 treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab and SEA-CD40 have been withheld, pembrolizumab and SEA-CD40 may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Immune-related AEs	Toxicity grade or conditions (NCI CTCAE v5.0)	Action with pembrolizumab and SEA-CD40	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	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) Subjects with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis 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
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased bilirubin	Grade 2[a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)

Immune-related AEs	Toxicity grade or conditions (NCI CTCAE v5.0)	Action with pembrolizumab and SEA-CD40	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
	Grade 3[b] or 4[c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for patients with T1DM Administer antihyperglycemic in subjects with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinued		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinued		
Hypothyroidism	Grade 2, 3, 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (NCI CTCAE v5.0)	Action with pembrolizumab and SEA-CD40	irAE management with corticosteroid and/or other therapies	Monitoring and follow-up
Myocarditis	Grade 2, 3, or 4	Permanently discontinue	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other irAEs	Persistent Grade 2	Withhold	Based on severity of AE, administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune-related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

a AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

b AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

c AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

d The decision to withhold or permanently discontinue pembrolizumab and/or SEA-CD40 is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

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

Restarting Study Drugs

If the toxicity does not resolve or the criteria for resuming treatment are not met, the subject must be discontinued from both SEA-CD40 and pembrolizumab.

If the toxicities do resolve and conditions are aligned with what is defined in Table 7, the combination of SEA-CD40 and pembrolizumab may be restarted at the discretion of the investigator.

In cases where the toxicity is attributed to SEA-CD40 but not pembrolizumab, re-initiation of pembrolizumab may be considered after communication with the sponsor. If toxicity is attributed to pembrolizumab but not SEA-CD40, re-initiation of SEA-CD40 may be considered after communication with the sponsor.

5.2.2. Dose Modifications SEA-CD40

Modifications to the 10 mcg/kg dose of SEA-CD40 will not be allowed.

Immune-related adverse events should be managed as outlined in Table 7. For non-immune SEA-CD40-related AEs for which more specific guidance does not exist elsewhere in the protocol:

For any SEA-CD40-related AE, determined to be clinically significant by an investigator, which is ongoing at the next scheduled dosing day, the dose may be delayed, at the discretion of the investigator, until resolution to baseline or ≤ Grade 1 in severity. If the AE is still ongoing on a subsequent scheduled dosing day, SEA-CD40 may be discontinued at the discretion of the investigator (consider consultation with the medical monitor).

For clinically significant Grade 3, SEA-CD40-related AEs ongoing at the next scheduled dosing day, the dose of SEA-CD40 should be held until the severity resolves to ≤ Grade 2 or returns to baseline. If the AE is still ongoing on a subsequent scheduled dosing day, SEA-CD40 may be discontinued at the discretion of the investigator (consider consultation with the medical monitor).

For Grade 4, life-threatening SEA-CD40 related AEs, SEA-CD40 should be permanently discontinued.

5.2.3. Dose Modifications Pembrolizumab

5.2.3.1. Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions 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 8.

Table 8: Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment Recommendations	Premedication at Subsequent Pembrolizumab 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 hrs	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs[a] 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/hr to 50 mL/hr). 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 pembrolizumab treatment.	Subject may be premedicated 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine) Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic)
Grades 3 or 4 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) Grade 4:	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs[a] Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	No subsequent pembrolizumab dosing

NCI CTCAE Grade	Treatment Recommendations	Premedication at Subsequent Pembrolizumab Dosing
Life-threatening; pressor or ventilatory support indicated	Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Subject is permanently discontinued from further pembrolizumab treatment.	

NSAID=non-steroidal anti-inflammatory drug
[a] For subjects in Cohorts 4 and 5, NSAIDs should not be administered in the timeframes outlined in Section 5.4.3
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the NCI CTCAE v5.0 at http://ctep.cancer.gov.

All Grade 3 or 4 events of IRR must be reported to the sponsor immediately, regardless of relationship to either SEA-CD40, pembrolizumab, or another study drug. All Grade 4 events are SAEs and are to be reported within the SAE reporting timeframe of 24 hours via the standard SAE forms (see Section 7.7.1.4).

5.2.3.2. Other Allowed Dose Interruptions and Modifications for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. If a subject in Cohorts 1, 2, or 3 is unable to receive the first dose of pembrolizumab in any given cycle and is considered appropriate to receive pembrolizumab as standard of care, the subject may receive a 200 mg dose of pembrolizumab on Day 29 to Day 31 of the cycle. The subject will then continue to receive pembrolizumab at Q6W as planned on Day 8 of the next cycle, as long as the subject continues to be appropriate to receive pembrolizumab. If a subject requires a longer interruption of pembrolizumab for reasons other than treatment-related AEs, study intervention should be restarted within 21 days (for Q3W dosing) or 42 days (for Q6W dosing) of the originally scheduled dose and within 42 days (for Q3W dosing) or 84 days (for Q6W dosing) of the previously administered dose, unless otherwise discussed with the sponsor. The reason for interruption is to be documented in the subject's study record.

5.2.4. Dose Modifications Pemetrexed/Carboplatin

Recommended dose modifications for selected pemetrexed and carboplatin toxicities are outlined in Table 9 and Table 10. Refer to the pemetrexed and carboplatin USPIs or local labels for full toxicity management guidelines.

Dose modifications must be based on the maximum toxicity experienced during a cycle. Toxicity must resolve to Grade ≤1 or baseline prior to resuming subsequent cycle. For individual subjects requiring a dose modification, treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to Grade ≤1 or the baseline status of the subject.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one agent. If, in the opinion of the investigator,

the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications.

Subjects may have chemotherapy discontinued and continue on SEA-CD40 and/or pembrolizumab.

Chemotherapy may be interrupted for a maximum of 6 weeks from last dose, unless otherwise discussed with the sponsor.

Table 9 and Table 10 serve as a guide, and do not replace investigator judgement and applicable local label recommendations if more stringent.

Table 9: Recommended Dose Modifications for Chemotherapy Hematological Toxicity

Platelets	ANC	Pemetrexed Dose	Carboplatin Dose
≥50,000/mcL AND	≥500/mcL	500 mg/m^2	AUC 5 Maximum dose 750 mg
≥50,000/mcL AND	<500/mcL	375 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
<50,000/mcL without bleeding AND	ANY	375 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
<50,000/mcL with Grade ≥2 bleeding AND	ANY	250 mg/m^2	AUC 2.5 Maximum dose 375 mg
ANY AND	<1000/mcL + fever ≥38.5°C (101°F)	375 mg/m^2	AUC 3.75 Maximum dose 562.5 mg

Table 10: Recommended Dose Modifications for Chemotherapy Non-Hematological Toxicity

Event	CTCAE Severity Grade	Pemetrexed Dose	Carboplatin Dose
Nausea or vomiting	Grade 3 or 4	500 mg/m^2	AUC 5 Maximum dose 750 mg
Diarrhea	Grade 3 or 4	375 mg/m^2	AUC 5 Maximum dose 750 mg
Mucositis	Grade 3 or 4	250 mg/m^2	AUC 5 Maximum dose 750 mg
Neurotoxicity	Grade 2	500 mg/m^2	AUC 5 Maximum dose 750 mg
	Grade 3 or 4	375 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
Transaminase elevation	Grade 3	375 mg/m^2	AUC 3.75 Maximum dose 562.5 mg
	Grade 4	Discontinue	Discontinue
Other non-hematological toxicity.	Grade 3 or 4	375 mg/m^2	AUC 3.75 Maximum dose 562.5 mg

5.3. Required Premedication and Postmedication

Prophylactic premedication for IHRs is required prior to administration of SEA-CD40. Premedication should include all of the following:

- Both H1 and H2 histamine receptor blockers
- Acetaminophen
- Ibuprofen or other NSAIDs (except in subjects in Cohorts 4 and 5 with CrCl <80 mL/min)
- Anti-emetic of choice for nausea/vomiting symptom control (excluding steroids)

For subjects who tolerate at least 2 consecutive cycles of SEA-CD40 treatment without a Grade 3 or higher IHR, one or all of the required premedications may be discontinued at the discretion of the investigator (consider consultation with the medical monitor).

For management of IHRs, see Section 5.5.1.

If consistent with local practices, it is recommended that corticosteroid pre-medication for pemetrexed comprise a single dose of dexamethasone IV 10–20 mg on Day 1 (Elsoueidi 2016; Clark 2019; Groleau 2020).

Antiemetic therapy should be consistent with Multinational Association of Supportive Care in Cancer (MASCC) guidelines (available at www.mascc.org/antiemetic-guidelines). When carboplatin is used during the first 4 cycles in subjects with NSCLC (Cohorts 4 and 5), antiemetic therapy should include a 5-HT3 receptor antagonist, dexamethasone, and an NK1 antagonist such as aprepitant per the MASCC guidelines on the day of carboplatin dosing.

Other than as specified above, use of prophylactic corticosteroids for chemotherapy dosing is discouraged unless clinically indicated due to the potential for corticosteroids to interfere with the mechanism of SEA-CD40. Consider medical monitor consultation if additional corticosteroid use is considered necessary in conjunction with chemotherapy, based on emerging toxicity or other considerations.

There are no required post-medications.

5.4. Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.4.1. Required Concomitant Therapy

Subjects receiving pemetrexed should receive folic acid and vitamin B12 supplementation as follows:

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

Required premedications for study drugs are described in Section 5.3.

5.4.2. Allowed Concomitant Therapy

The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed. The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy.

Concomitant prednisone (or equivalent) may be used at physiologic-replacement dose levels when clinically indicated. Intermittent high-dose corticosteroid treatment to prevent or manage hypersensitivity reactions (including premedication for known hypersensitivity reactions to contrast for radiographic assessments) may be used at the investigator's discretion. Intermittent high-dose corticosteroid treatment for other reasons, including management of immune-mediated AEs, may be used at the investigator's discretion.

The use of antibiotics including prophylactics, when applicable, is allowed.

The use of bone modifying agents, when applicable, is allowed.

Study treatment may be interrupted by palliative radiotherapy not involving target lesions, at the investigator's discretion.

Routine prophylaxis with vaccines is permitted; it is recommended that vaccines used do not contain live microorganisms.

5.4.3. Prohibited Concomitant Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy (other than palliative radiotherapy, see Section 5.4.2), or systemic anti-neoplastic therapy during the study. Immunosuppressive medications, such as steroids, may not be used as prophylaxis for IRRs on days where SEA-CD40 is administered.

The following additional therapies are prohibited for Cohorts 4 and 5 only:

- Yellow fever vaccines
- Ibuprofen or other NSAIDs (including premedication) in subjects with CrCl <80 mL/min, during the 2 days before, the day of, and 2 days after pemetrexed administration
- Long acting NSAIDs (such as piroxicam or rofecoxib) for 5 days before, the day of, and 2 days after pemetrexed administration.

5.5. Management of Treatment-Emergent Adverse Events

5.5.1. Management of Infusion/Injection or Hypersensitivity Reactions

5.5.1.1. SEA-CD40

IHRs, including CRS, have been observed in subjects administered SEA-CD40. The most common IRR-related symptoms were chills, nausea, and vomiting; onset of symptoms typically occurred within 2 hours, and in some cases within minutes after starting SEA-CD40 and resolved within a few hours after discontinuation of the infusion and symptomatic treatment (ie, antihistamines, antiemetics, antipyretics, opioids, and/or corticosteroids). If any such events occur during therapy with SEA-CD40, supportive care is advised.

Required SEA-CD40 premedications for IHRs and possible CRS are described in Section 5.3.

Recommendations for management of IHRs associated with SEA-CD40 are detailed in Table 11.

Table 11: Treatment Recommendations and Dose Modifications for SEA-CD40 Infusion/Injection or Hypersensitivity Reactions

NCI CTCAE		Treatment Recommendations	Dose Modifications
Grade 1	Mild reaction; SEA-CD40 treatment interruption not indicated; intervention not indicated. Transient flushing or rash, drug fever <38°C (<100.4°F); or intervention not indicated.	Monitor vital signs more frequently until symptoms have resolved and subject is medically stable. Administer symptomatic treatment as medically indicated.	Consider additional premedication with subsequent SEA-CD40 treatment if clinically indicated.
Grade 2	SEA-CD40 treatment interruption indicated but responds promptly to symptomatic treatment (ie, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	Hold SEA-CD40 treatment. Monitor vital signs more frequently and administer symptomatic treatment as medically indicated. If subject responds promptly and is medically stable in the opinion of the investigator, SEA-CD40 treatment may be continued, potentially at a slower rate.	Consider additional premedication and/or slower infusion rate with subsequent SEA-CD40 treatment. If subject has adrenal insufficiency, consider increasing replacement steroid dose to 10 mg prednisone equivalent per day on SEA-CD40 dosing days.
Grade 3[a]	Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of SEA-CD40 treatment); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (ie, renal impairment, pulmonary infiltrates).	Stop SEA-CD40 treatment. Appropriate additional medical therapy should be instituted. Consider hospitalization.	Subjects with an IHR that resolves to baseline or ≤ Grade 1 within approximately 2 hours after intervention may continue on SEA-CD40 treatment at the investigator's judgement. The possibility of additional pre-medication and/or slowed infusion rate may be discussed with the medical monitor OR Permanently discontinue from study treatment.
Grade 4[a]	Life-threatening consequences; urgent intervention indicated; pressor or ventilator support indicated	Stop SEA-CD40 treatment immediately. Hospitalization.	Permanently discontinue from study treatment.

[a] All Grade 3 or 4 events of IHR must be reported to the sponsor immediately, regardless of relationship to study drugs. All Grade 4 events are SAEs and are to be reported within the SAE reporting timeframe of 24 hours via the standard SAE forms (see Section 7.7.1.4).

5.5.2. Allergic/Hypersensitivity Reaction

Allergic/hypersensitivity reactions are characterized by adverse local or general responses from exposure to an allergen (NCI CTCAE, v5.0). For purposes of this study, allergic/hypersensitivity reactions are differentiated from IRRs by being defined as occurring >24 hours after infusion of the study drug. Allergic/hypersensitivity reactions may manifest in the same manner as IRRs (ie,

a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rash, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension).

Required SEA-CD40 premedications are described in Section 5.3.

Allowed measures include dose modifications (Section 5.2) and concomitant medications (Section 5.4).

5.5.2.1. Anaphylaxis

Anaphylaxis is a severe, life-threatening, generalized or systemic allergic/hypersensitivity reaction. Anaphylaxis is characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death (NCI CTCAE, v5.0 and (Rosello 2017).

If anaphylaxis occurs, administration of the study drug should be immediately and permanently discontinued.

5.5.3. Management of Overdose

SEA-CD40

An overdose of SEA-CD40 is defined as ≥10% of the intended dose. In the event of an overdose of SEA-CD40, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of SEA-CD40.
- Notify the medical monitor as soon as they become aware of the overdose, to discuss details of the overdose (eg, exact amount of SEA-CD40 administered, subject weight) and AEs, if any.

Pembrolizumab

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

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. The overdose should be reported to the sponsor within 24 hours of observing or learning of the overdose.

Pemetrexed and Carboplatin

In the event of an overdose of pemetrexed and/or carboplatin, the event should be managed according to the product label and/or institutional standard of care, and promptly reported to the sponsor.

5.5.4. Management of Ocular Events

Investigators should monitor subjects closely for any type of ocular symptoms that could be immune-mediated. If a subject has a persistent Grade 2 or higher ocular event that is suspected to be immune-mediated, the investigator should hold pembrolizumab and/or SEA-CD40 in accordance with Table 7 and refer the subject for ophthalmologic examination.

5.6. Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF. In the event of an overdose ≥10%, the site should notify the sponsor or designee as soon as they are aware of the overdose.

5.7. Continued Access to SEA-CD40 After the End of the Study

A subject deriving clinical benefit from SEA-CD40 at the time the study is completed may be permitted to continue to receive SEA-CD40, provided the investigator considers it to be in the subject's best individual treatment option and the study was not terminated due to safety concerns. Requests will be discussed on a subject-by-subject basis with the sponsor. If continued access to SEA-CD40 is permitted, sparse data may be collected to monitor the safety and tolerability of continued administration (see Section 3.1.5)

5.8. Visit Scheduling for Single Treatment Discontinuation

Each time a subject discontinues a component of combination therapy but is continuing with another component, clinic visits and safety assessments (including pregnancy testing) associated with the discontinued treatment may be moved or eliminated (if considered appropriate after consultation with the medical monitor), if there are no other study drugs administered on that day. If biomarker/patient-reported outcome (PRO) assessments fall on a day that no longer has any study drug administered, these may be moved to the next scheduled visit or eliminated, if considered appropriate after consultation with the medical monitor.

6. STUDY ACTIVITIES

6.1. Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.7.1.3). Any study protocol-related AE (defined in Section 7.7.1.1) as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (chemistry panel, complete blood count [CBC] with differential [manual differential if clinically indicated], thyroid panel, and urinalysis including urine protein creatinine ratio (UPC) ratio [with reflexive microscopy for abnormal results]), physical examination, weight, and ECOG performance status may be performed within 3 days prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing.

Day 1 of Cycles 2 and beyond may be delayed by up to 4 days for administrative reasons (ie, holidays or scheduling conflicts).

Schedule of Events tables are provided:

- Table 1: Schedule of Events for Cohorts 1, 2, and 3 (Melanoma)
- Table 2: Schedule of Events for Cohorts 4 and 5 (NSCLC)

Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

Note: Any samples and data collection for exploratory objectives which are not necessary to evaluate any primary and secondary objective can be discontinued at the discretion of the sponsor (for example, but not limited to: PROs, SEA-CD40 PK, CD40 antidrug antibody [ADA], Plasma, PD flow, Tumor biopsy, Genotyping, Serum, PBMC, cell-free DNA [cfDNA]).

6.2. Cohorts 1, 2, and 3 (Melanoma)

6.2.1. Screening Visit (Days –28 to 1)

- Informed consent
- Medical history
- Study eligibility per inclusion/exclusion criteria
- Height (height measured within the prior 12 months may be utilized)
- MRI scan of the brain. If an MRI is not medically feasible, a CT scan may be done instead.
- Blood sample collection for
    - Thyroid panel
    - Hgb A1c
- ECG
- Diagnostic-quality CT and/or MRI of the chest, abdomen, and pelvis (as well as brain and/or neck if documented or suspected involvement in these regions), with IV contrast unless medically contraindicated (Section 7.2)
- PRO assessment, European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) (for subjects entered in the study after enrollment for the interim analysis is completed)
- PRO collections may be discontinued at the discretion of sponsor.
    - Procedures conducted as part of the subject's routine clinical management (eg, thyroid panel) and before signing of the informed consent may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the Schedule of Events.

Subjects may be rescreened once. If rescreening is conducted outside of the 28-day screening period, a new subject number will be assigned.

6.2.2. Baseline Visit

Baseline events and assessments should be performed on Study Day –7 to Day 1 unless otherwise specified.

- Physical examination including weight
- ECOG performance status (Appendix A)
- Vital signs
- Blood sample collection for biomarker assessments (window of collection is Day –7 to –1; Table 3)
- Blood or urine sample collection for serum or urine β-hCG pregnancy test for subjects of childbearing potential (window of collection is Day –3 to Day 1; Section 7.7.6)
- Blood and urine sample collection for (Section 7.7.3):
    - CBC with differential
    - Chemistry panel
    - Prothrombin time/activated partial thromboplastin time/international normalized ratio (PT/aPTT/INR)
    - Urinalysis
- PRO collections (may be discontinued at the discretion of sponsor.)
- Initiate retrieval of archived tumor biopsy specimen for submission upon enrollment (Section 7.4)
    - For subjects entered in the study after completion of enrollment for the interim analysis in each of Cohorts 1 and 2, archived tumor specimen must have been collected from the subject within 30 days prior to anticipated first dose of study drug. If the archived tumor sample is older than 30 days, a baseline tumor biopsy is required.

6.2.3. Treatment Period (Day 1 to Day 42)

6.2.3.1. Day 1 (±2 days)

- Prior to SEA-CD40 administration:
    - Confirm subject eligibility per inclusion/exclusion criteria (Cycle 1 only)
    - Physical examination*
    - Weight*
    - Vital signs (within 30 minutes prior to SEA-CD40 administration)
    - ECOG performance status (Appendix A)
    - ECG (Cycle 1 and 2 only; first 30 subjects at US sites across Cohorts 1, 2, and 3 performed prior to PK sample collection at corresponding time points; see Table 4)

- Blood and/or urine sample collection for (Section 7.7.3):
  - CBC with differential*
  - Chemistry panel*
  - Thyroid panel*
  - PK/antidrug body (ADA) assessments (Table 3)
  - Biomarker assessments (Section 7.4; Table 3)
  - Urinalysis (Cycle 3 and every 3 cycles thereafter)*
  - Serum or urine β-hCG pregnancy test (only subjects of childbearing potential; not required if collected within 7 days prior to dosing)
- PRO assessment, EORTC QLQ-C30 (for subjects entered in the study after enrollment for the interim analysis is completed; for Cycle 1 (EORTC QLQ-C30; Non-Small Cell Lung Cancer Symptom Assessment Questionnaire [NSCLC-SAQ) and Cycle 2 (Patient Global Impression of Symptom Change [PGI-C) and every cycle thereafter)
  - PRO collections may be discontinued at the discretion of sponsor.
- Results from clinical laboratory assessments must be reviewed and must confirm eligibility prior to study drug infusion
- SEA-CD40 infusion
- During SEA-CD40 infusion
  - Blood sample collection for PK assessments (Cycles 1 and 2 only)
    - 1-hour intra-dose
    - 2-hours intra-dose
- After completion of SEA-CD40 administration:
  - Vital signs (within 30 minutes after the end of SEA-CD40 infusion)
  - Blood sample for PK assessments (Cycles 1 and 2 only; Table 3)
  - ECG for the first 30 subjects across Cohorts 1, 2, and 3 performed prior to PK sample collection at corresponding time points (Cycles 1 and 2 only;

* Indicated assessments may be collected within 3 days prior to dosing.

6.2.3.2. Day 2 (Cycles 1 and 2 only)

- ECG (first 30 subjects at US sites across Cohorts 1, 2, and 3 performed prior to PK sample collection at corresponding time points) (Table 4)
- Blood sample for PK and biomarker assessments (Table 3)

6.2.3.3. Day 8 (±2 days)

- Before pembrolizumab infusion

- Vital signs (within 30 minutes prior to pembrolizumab administration)
- CBC with differential (may be collected within 3 days prior to dosing)
- Chemistry panel (may be collected within 3 days prior to dosing)
- Results from clinical laboratory assessments must be reviewed and must confirm eligibility prior to study drug infusion

- Pembrolizumab infusion
- After completion of pembrolizumab administration:
  - Vital signs (within 30 minutes after the end of pembrolizumab infusion)

6.2.3.4. Day 22 (±2 days)

- Before SEA-CD40 infusion
  - Vital signs (within 30 minutes prior to SEA-CD40 administration)
  - Blood sample collection for
    - CBC with differential (may be collected within 3 days prior to dosing)
    - Chemistry panel (may be collected within 3 days prior to dosing)
    - Blood sample for PK and biomarker assessments (Cycles 1 and 2 only; Table 3)
    - Serum or urine β-hCG pregnancy test (only subjects of childbearing potential; not required if collected within 7 days prior to dosing)
    - Results from clinical laboratory assessments must be reviewed and must confirm eligibility prior to study drug infusion
- SEA-CD40 infusion
- After SEA-CD40 infusion
  - Vital signs (within 30 minutes after the end of SEA-CD40 infusion)
  - Blood sample for PK assessment (Cycles 1 and 2 only; Table 3)

6.2.3.5. Day 36 (–2/+5 days; Cycle 1 only)

- Tumor biopsy is required for subjects entered in the study after completion of enrollment for the interim analysis in Cohorts 1 and 2. This biopsy is optional for all other subjects. The same tumor site should be biopsied for the baseline and on-treatment biopsies.

6.2.4. Response Assessments

- CT and/or MRI of the chest, abdomen, and pelvis (as well as brain and/or neck if documented or suspected involvement in these regions) Q6W [±3 days] from Cycle 1 Day 1, regardless of dose delays, for the first 24 weeks. After 24 weeks, imaging will be required every 12 weeks (± 1 week) until documentation of PD (confirmed

progressive disease [iCPD] per iRECIST), initiation of subsequent anti-cancer therapy, study termination by the sponsor, or death, whichever occurs first. Scans must be of diagnostic quality and IV contrast must be used unless medically contraindicated. For each assessed lesion, the same modality should be used throughout the duration of the study.

6.3. Cohorts 4 and 5 (NSCLC)

6.3.1. Screening Visit (Days –28 to 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- Height (height measured within the prior 12 months may be utilized)
- MRI scan of the brain. If an MRI is not medically feasible, a CT scan may be done instead.
- Blood sample collection for
    - Thyroid panel
    - Hgb A1c
- Vital signs
- ECG
- Diagnostic-quality CT and/or MRI of the chest and abdomen (and pelvis, neck, and/or brain if documented or suspected involvement in these regions), with IV contrast unless medically contraindicated (Section 7.2)

6.3.2. Baseline Visit

Baseline events and assessments should be performed on Study Day –7 to Day 1 unless otherwise specified.

- Physical examination including weight
- ECOG performance status (Appendix A)
- Blood sample collection for biomarker assessments (window of collection is Day –7 to –1; Table 5)
- Blood or urine sample collection for serum or urine β-hCG pregnancy test for subjects of childbearing potential (window of collection is Day –3 to Day 1; Section 7.7.6)
- Blood and urine sample collection for (Section 7.7.3):
    - CBC with differential
    - Chemistry panel
    - PT/aPTT/INR

- Urinalysis

- Initiate retrieval of archived tumor biopsy specimen for submission upon enrollment (Section 7.4)
- PRO assessment (for subjects entered in the study after enrollment for the interim analysis is completed) EORTC QLQ-C30
  - Patient Global Impression of Symptom Severity (PGI-S).
  - PRO collections may be discontinued at the discretion of sponsor.
  - NSCLC-SAQ

6.3.3. Treatment Period (Day 1 to Day 21)

6.3.3.1. Day 1 (±2 days)

- Prior to study drug administration:
  - Confirm subject eligibility per inclusion/exclusion criteria (Cycle 1 only)
  - Physical examination*
  - Weight*
  - Vital signs (within 30 minutes prior to the start of the first study drug administration)
  - ECOG performance status (Appendix A)*
  - Blood and/or urine sample collection for (Section 7.7.3):
    - CBC with differential*
    - Chemistry panel*
    - Thyroid panel (Cycle 1 and every second cycle thereafter)*
    - Blood sample for PK/ADA assessments (Cycles 1, 2, 3, 4, 6, and 8 only; Table 5)
    - Blood samples for biomarker assessments (Section 7.4; Table 5)
    - Urinalysis (Cycle 6 and every 6 cycles thereafter)*
    - Serum or urine β-hCG pregnancy test (only subjects of childbearing potential) (in Cycle 1, not required if performed within 3 days prior to visit. In all other cycles, not required if performed within 7 days prior to visit.)
  - PRO assessments (for subjects entered in the study after enrollment for the interim analysis is completed; for Cycle 1 [EORTC QLQ-C30; NSCLC-SAQ] and Cycle 2 [PGI-C] and every cycle thereafter)
    - EORTC QLQ-C30
    - NSCLC-SAQ

        - PGI-C
    - Results from clinical laboratory assessments must be reviewed and must confirm eligibility prior to study drug infusion
- Pembrolizumab administration
- Pemetrexed administration
- Carboplatin administration (Cycles 1–4 only)
- After study drug administration:
    - Vital signs (within 30 minutes after the end of the last study drug administration)

* Indicated assessments may be collected within 3 days prior to dosing.

6.3.3.2. Day 3

- Before SEA-CD40 infusion
    - Blood sample collection for PK/ADA and biomarker assessments (Cycles 1 and 2 only; Table 5)
    - Vital signs (within 30 minutes prior to SEA-CD40 administration)
- Blood sample collection for
    - CBC with differential
    - Chemistry panel
- SEA-CD40 infusion
    - Observation is required following infusion (see Section 5.1.1.2)
    - Intra-dose and post-dose blood sample collection for PK assessment (Cycles 1 and 2 only; Table 5)
- After completion of SEA-CD40 administration:
    - Vital signs (within 30 minutes after the end of SEA-CD40 infusion)

6.3.3.3. Day 4 (Cycles 1 and 2 only)

- Blood sample collection for PK and biomarker assessments (Table 5)

6.3.3.4. Day 15 (–2/+5 days; Cycle 2 only)

- Optional tumor biopsy. The same tumor site should be biopsied for baseline and on-treatment biopsies.

6.3.4. Response Assessments

- CT and/or MRI of the chest and abdomen (and pelvis, neck, and/or brain if documented or suspected involvement in these regions) Q6W [±3 days] from Cycle 1 Day 1, regardless of dose delays, for the first 24 weeks. After 24 weeks, imaging will

be required every 12 weeks (±1 week) until documentation of PD (iCPD per iRECIST), initiation of subsequent anti-cancer therapy, study termination by the sponsor, or death, whichever occurs first. Scans must be of diagnostic quality and IV contrast must be used unless medically contraindicated. For each assessed lesion, the same modality should be used throughout the duration of the study.

Note: Any samples and data collection for exploratory objectives which are not necessary to evaluate any primary and secondary objective can be discontinued at the discretion of the sponsor (for example, but not limited to: PROs, SEA-CD40 PK, CD40 ADA, Plasma, PD flow, Tumor biopsy, Genotyping, Serum, PBMC, cfDNA).

6.4. End of Treatment Visit (30 to 37 days after last dose of study drug; all cohorts)

End of treatment (EOT) visits should occur 30 to 37 days after the last dose of study drug unless delayed due to an AE. Note: The time to EOT visit may be longer than 37 days, but in no case should it be <30 days. However, EOT evaluations must be performed before initiation of a new anticancer treatment. If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted 30 to 37 days following the last treatment to assess for AEs.

- ECOG performance status (Appendix A)
- Physical examination including weight
- CBC with differential
- Chemistry panel
- Thyroid panel
- Hgb A1c
- Vital signs
- PT/aPTT/INR
- Serum or urine β-hCG pregnancy test (only subjects of childbearing potential)
- ECG
- Blood sample for PK/ADA assessments (Section 7.4)
- Blood samples for biomarker assessments (Section 7.4)
- For subjects discontinuing treatment due to disease progression: if a tumor biopsy was performed per standard of care at the time of disease progression, submit sample of tumor specimen, if available (see Section 7.4)
- **Cohorts 1, 2, and 3:** Diagnostic-quality CT or MRI of chest, abdomen, and pelvis (plus neck and/or brain if documented or suspected involvement in these regions), with IV contrast unless medically contraindicated (not required if done 4 weeks prior to EOT; Section 7.2)

- **Cohorts 4 and 5:** Diagnostic-quality CT or MRI of chest and abdomen (plus pelvis, neck, and/or brain if documented or suspected involvement in these regions), with IV contrast unless medically contraindicated (not required if done 4 weeks prior to EOT; Section 7.2)
- PRO Assessments (for subjects enrolled in the study after enrollment for the interim analysis is completed). PRO collections may be discontinued at the discretion of sponsor.
    - EORTC QLQ-C30
    - NSCLC-SAQ (Cohorts 4 and 5 only)
    - PGI-S (Cohorts 4 and 5 only)

6.5. Follow-up (all cohorts)

The first follow-up visit will occur 12 weeks (±1 week) (unless otherwise stated) from the most recent prior response evaluation. Subsequent follow-up visits will be scheduled for 12 weeks (±1 week) from the previous follow-up visit. Subjects will be followed at this schedule until withdrawal of consent, death, or study closure, whichever occurs first.

Subjects who discontinue treatment will continue to be assessed for response after EOT until confirmed PD or initiation of new anticancer treatment. After SEA-CD40 drug expiry, response assessment in these patients may be continued per standard of care (SoC) at the discretion of the investigator. Subjects who discontinue treatment due to confirmed PD or who have initiated new anticancer treatment will not be assessed for response but will be followed for survival and subsequent anticancer treatment. Follow-up may be conducted with clinic visits or telephone calls. Survival follow-up may be discontinued at the discretion of sponsor.

The following assessments will be performed until confirmed disease progression or initiation of subsequent anticancer treatment; subjects will be followed for survival and subsequent anticancer treatment thereafter.

- Physical examination
- Serum or urine β-hCG pregnancy test (only subjects of childbearing potential). Subjects may do home pregnancy tests and report interim results at the follow-up visits.
    - Cohorts 1, 2, and 3: performed monthly for 120 days after the last received dose of study drug, or per local regulations, where applicable.
    - Cohorts 4 and 5: performed monthly for 6 months after the last received dose of study drug, or per local regulations, where applicable.
- Diagnostic-quality CT and/or MRI with IV contrast unless medically contraindicated
    - Cohorts 1, 2, and 3: chest, abdomen, and pelvis (as well as brain and/or neck if documented or suspected involvement in these regions).
    - Cohorts 4 and 5: chest and abdomen (as well as pelvis, brain and/or neck if documented or suspected involvement in these regions).

- Collection of AEs if serious and considered to be related to study treatment (except as outlined below)
- Disease status
- Survival status
- Collection of first subsequent anticancer treatment

In addition, the following will be performed at the first follow-up visit only:

- Chemistry panel
- Thyroid panel
- Collection of all SAEs for 90 days after the last dose of study treatment and collection of all irAEs (except as outlined in Section 7.7.1.3).

6.6. Survival Follow-up (all cohorts)

All subjects will be followed for long-term survival. Assessment of survival can be done via public or hospital/medical records or a phone call. After disease progression or initiation of a new anticancer treatment, survival follow-up will be conducted, at the discretion of the sponsor, every 12 weeks (±1 week) for survival status until death or study closure, whichever comes first. During this time, if a new anticancer treatment is initiated, information regarding the first anticancer therapy subsequent to discontinuing study treatment will be collected.

The first survival follow-up will occur 12 weeks (±1 week) (unless otherwise stated) from the last radiographic scan that demonstrated disease progression or from initiation of the new anticancer treatment, as applicable. Subsequent survival follow-up will be scheduled for 12 weeks (±1 week) (unless otherwise stated) from the previous survival follow-up. Timing of subsequent survival follow-up may be modified, or collection will be stopped, at the discretion of sponsor.

6.7. End of Follow-up (all cohorts)

The date the subject met criteria for study discontinuation and the reason for study discontinuation will be recorded.

7. STUDY ASSESSMENTS

7.1. Screening/Baseline Assessments

Only subjects who meet the eligibility criteria specified in Section 4 will be enrolled in this study.

Subject medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Weight and height will also be measured; measurements of height obtained within the prior 12 months may be utilized (Section 7.7.4).

Blood and urine tests will include CBC with differential, chemistry panel, thyroid panel, Hgb A1c, PT/aPTT/INR, and urinalysis. A serum or urine β-hCG pregnancy test will be conducted for subjects of childbearing potential (Section 4.3). Spot urine UPC ratio calculation is sufficient. Further details of these tests are provided in Section 7.7.3.

Blood samples and tumor biopsies will be collected for biomarker assessments (see Section 7.4).

An MRI of the brain will be performed at screening. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

An ECG will be performed at screening and at EOT for all subjects (Section 7.7.5). Additional on-treatment ECGs will be collected for select subjects (Table 4).

7.2. Response/Antitumor Activity Assessments

The determination of antitumor activity will be based on objective response assessments as defined by RECIST v1.1 (Eisenhauer 2009) and iRECIST (Seymour 2017) (Appendix D). Treatment decisions by the investigator will be based on iRECIST. Clinical response of PD, SD, partial response (PR), or complete response (CR) will be determined at each assessment.

Response will be assessed by radiographic tumor evaluation Q6W (±3 days) for the first 24 weeks and every 12 weeks (±1 week) thereafter through documentation of PD (iCPD per iRECIST), initiation of subsequent anti-cancer therapy, study termination by the sponsor, or death, whichever occurs first. Tumor evaluation will be performed by CT and/or MRI scan of the chest and abdomen (and pelvis for Cohorts 1, 2, and 3). Imaging of the pelvis, neck, and/or brain must also be obtained if there is documented or suspected involvement in these regions. If brain scans are performed, MRI is preferred; however, CT scans are acceptable if MRI is medically contraindicated. Scans must be of diagnostic quality and IV contrast must be used unless medically contraindicated. For each assessed lesion, the same modality should be used throughout the duration of the study.

Subjects' clinical data must be available for CRF source verification. Copies of all tumor images must be made after acquisition and forwarded to the sponsor/designee as per the instructions provided in the central imaging manual.

7.3. Pharmacokinetic and Immunogenicity Assessments

Blood samples for SEA-CD40 PK (plasma) and ADA (serum) analyses will be collected throughout the study per the sample collection schedules provided in Table 3 and Table 5. Sensitive, validated assays will be used to measure SEA-CD40 concentrations in plasma and ADA in serum. PK parameters for SEA-CD40 to be estimated may include, but are not limited to, AUC and C_{max} in plasma. Any samples and data collection for exploratory objectives which are not necessary to evaluate any primary and secondary objective can be discontinued at the discretion of the sponsor (for example, but not limited to: PROs, SEA-CD40 PK, CD40 ADA, Plasma, PD flow, Tumor biopsy, Genotyping, Serum, PBMC, cfDNA).

7.4. Pharmacodynamic and Biomarker Assessments

Biomarker assessments will be performed in peripheral blood and tumor tissue as outlined in this section, Table 3, and Table 5. Exploratory, predictive, and prognostic biomarkers associated with response, resistance, or safety observations will be monitored before and during treatment with

SEA-CD40. Biomarker assessments may be discontinued at any point at the sponsors discretion. Pharmacodynamic assessments will include flow cytometry evaluation of circulating immune subsets, such as but not limited to B cells, T cells, monocytes, DC, and NK cells. Cytokine levels in peripheral blood will also be assessed. Correlative studies will be conducted to gain a better understanding of target-response relationship, predictive/prognostic biomarkers, MOA, resistance mechanisms, and pharmacodynamics. On-treatment biopsies in a subset of subjects will be used to investigate the MOA of SEA-CD40.

Archival tumor should be collected for all subjects. Tumor tissue should be from locations not radiated prior to biopsy; formalin fixed specimens after the subject has been diagnosed with metastatic disease are preferred. Biopsies obtained prior to receipt of adjuvant/neoadjuvant chemotherapy will be permitted if recent biopsy is not feasible. If an archival tumor sample is not available, a fresh baseline biopsy is required.

After enrollment for the interim analysis is complete in Cohorts 1 and 2, on-treatment biopsies will be required for subsequent subjects in Cohorts 1 and 2. On-treatment biopsies are optional for all other subjects. For subjects from whom an on-treatment biopsy will be collected, the archival biopsy must have been collected within 30 days prior to the anticipated first dose of study drug; otherwise, a fresh baseline biopsy is required. If a tumor sample is obtained as part of standard of care during the study, a part of that sample should be submitted to the sponsor for biomarker testing. Biopsies should be collected by appropriately trained clinical site personnel (eg, an interventional radiologist for internal tumor biopsies; trained personnel such as a dermatologist for cutaneous tumor biopsies). It is strongly recommended that a pathologist be present during biopsies when feasible to ensure sufficient tumor content of the biopsy location, and to confirm that biopsy acquisition and processing techniques are optimal (Ferry-Galow 2018).

The immune modulatory effects of SEA-CD40 may lead to changes in the activation state of local, tumor-associated, and peripheral immune cells. To characterize the malignancy and immune response, biomarker assessments in peripheral blood may include, but are not limited to, measurement of baseline and drug-induced changes in circulating blood cell populations, cytokine/chemokines, gene expression, cytogenetics, genetic polymorphisms, somatic mutations associated with cancer, and circulating immune function and disease markers. SEA-CD40 interactions with peripheral blood cells and tissues may also be monitored. Assays may include, but are not limited to, next generation sequencing of whole blood, proteomic methodologies, immunoassays as a marker of tumor response or therapy resistance, and markers of immune function, including abundance of immune cell subsets and cytokines. Methods of analysis may include, but are not limited to, IHC, next generation sequencing of RNA and DNA, and immunoassays such as flow cytometry and enzyme-linked immunosorbent assay (ELISA). These may provide insight into treatment-related changes associated with SEA-CD40.

To understand the relationship between the biological characteristics of tumors before treatment and subject outcomes, tissue from pre-treatment (archival or freshly obtained specimens) and on-treatment tumor biopsies (for a subset of subjects) will be examined. If tissue is available from a standard clinical care biopsy collected after enrollment, it may also be examined. Biopsies will be assessed for specific pharmacodynamic, predictive, and prognostic biomarkers in the tumor. To characterize the malignancy and response to study treatment, biomarker assessments in tumor biospecimens may include, but are not limited to, measurements of SEA-CD40 and its

potential metabolites as well as characterization of the tumor microenvironment including PD-L1 expression, drug target(s), tumor subtyping, profiling of somatic mutations and/or gene expression. Assays may include, but are not limited to, IHC and next generation sequencing of RNA and DNA.

7.5. Biospecimen Repository

In the US only, for subjects who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Seagen and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.6. Patient-Reported Outcomes Assessments

After enrollment for the interim analysis is complete in a cohort, PROs will be administered to all subsequent subjects in that cohort to characterize the clinical profile of SEA-CD40 more fully in combination with other treatments. PROs will be administered at time points specified in Section 6, Table 1, and Table 2. PRO collections may be discontinued at the discretion of sponsor.

PRO data will be obtained through use of the following instruments:

- All cohorts: EORTC QLQ-C30
- Cohorts 4 and 5 only (NSCLC): NSCLC-SAQ, PGI-S, and PGI-C

The EORTC QLQ-C30 is a validated, reliable self-reported measure (Aaronson 1993) (Fitzsimmons 1999) (see Appendix F). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/QoL, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. The EORTC QLQ-C30 module takes approximately 10 minutes to complete. Each score is transformed onto a 0 to 100-point scale. In the 5 functional scales and the global health status scale, a high score means a "high level of functioning or global health status." For the symptom scales and single items, a higher score implies a "high level of symptoms or problems." Previously published minimally important differences will be used to identify meaningful changes from baseline in each treatment group on the disease and treatment-related symptom scales (Osoba 1998).

The NSCLC-SAQ was developed to assess symptoms of NSCLC in clinical trials in alignment with FDA recommendations and included input from subjects with NSCLC (McCarrier 2016), see Appendix G). The NSCLC-SAQ questionnaire is a 7-item PRO instrument that assesses intensity of cough and pain symptoms and frequency of dyspnea, fatigue, and appetite. The 7 questions of this instrument, which uses a 7-day recall period, are on a verbal rating scale from either "No <symptom> at all" (a score of 0) to "Very severe <symptom>" (a score of 4) for intensity questions or from "Never" (a score of 0) to "Always" (a score of 4) for frequency questions (FDA COA). NSCLC-SAQ will be administered at baseline, on Day 1 of each

treatment cycle, and at EOT to subjects enrolled in Cohorts 4 and 5 after completion of enrollment for the interim analysis. Symptom domains and total scores will be calculated according to the scoring manual and will be described in substudy protocols.

The PGI-S and the PGI-C are single-question 5-point scales used to assess general symptom severity and symptom change over time (see Appendix H and Appendix I for examples).

Subjects will use an application on a smartphone or tablet device to complete PRO assessments. Subjects will be provided a device or may use their own device if appropriate. Instructions and training on completing the PRO will be provided to the subject by the site staff. The data will be transmitted via a prespecified transmission method (eg, cellular or wifi networks) automatically after entry to a centralized database at the PRO vendor. The data can be accessed by appropriate study personnel securely via the internet.

The PRO instruments will be translated as appropriate in the country language(s) and as feasible in the local language. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be scheduled to be completed by the subject during a clinic visit before the subject receives any information on disease status and prior to any non-PRO assessments and the administration of study treatment.

7.7. Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication, and measurements of protocol-specified physical examination findings, vital signs, protocol-specified laboratory tests, ECOG status, ECGs, and pregnancy testing.

Safety will be monitored over the course of the study by an SMC as described in Section 3.1.7 and Section 9.3.10.

7.7.1. Adverse Events

7.7.1.1. Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, investigational new drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a subject or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the AEs CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 that increase in NCI CTCAE grade should be recorded.

- Medical conditions present or ongoing predose on study Day 1 that worsen in severity, increase in frequency, become related to study drug, or worsen in any other way but do not meet the threshold for increase in NCI CTCAE grade should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and postdose) through the end of the safety reporting period (see Section 7.7.1.3). Complications that occur in association with any procedure (eg, biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (eg, record "anemia" rather than "low hemoglobin").

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an

infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.7.1.2 for the definition of potential DILI).

Adverse Event Severity

AE severity should be graded using the NCI CTCAE, v5.0. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to each study treatment (SEA-CD40, pembrolizumab, pemetrexed, carboplatin) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture)
Unrelated:	Another cause of the AE is more plausible (eg, due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

7.7.1.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the AEs CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity

- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For IHRs, record the NCI CTCAE terms of 'cytokine release syndrome,' 'infusion related reaction,' 'allergic or hypersensitivity reaction,' or 'anaphylaxis' with an overall level of severity (per NCI CTCAE; see Table 11). In addition, record each sign or symptom of the reaction as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. 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. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be reported as AEs or SAEs.

Pregnancy

Notification to Drug Safety

Complete a Pregnancy Report Form for all pregnancies, including any pregnancies that occur in the partner of a study subject who can get someone pregnant, that occur from the time of first study drug dose until the end of the following time periods, as applicable:

- Cohorts 1, 2, and 3:
    - Subjects of childbearing potential, as defined in Section 4.3: 120 days after the last dose of study drug or 30 days after the last dose of study drug if the subject initiates a new anticancer therapy
    - Subjects who can get someone pregnant, as defined in Section 4.3: until the last dose of study drug
- Cohorts 4 and 5:
    - All subjects: 6 months after the last dose of study drug

Only report pregnancies that occur in a subject's partner if the estimated date of conception is after the subject's first study drug dose. Email or fax to the sponsor's Drug Safety Department within 24 hours of becoming aware of a pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks.

Collection of Data on the CRF

All pregnancies (as described above) will also be recorded on the AEs CRF.

Abortion, whether accidental, therapeutic, or spontaneous, should be reported as an SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.7.1.1) should be reported as SAEs.

Potential Drug-Induced Liver Injury

Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for potential DILI in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

Definition

Briefly, potential Hy's Law cases include the following 3 components:

1. Aminotransferase (ALT and/or AST) elevation >3 x ULN

AND

2. Total bilirubin >2 x ULN, without initial findings of cholestasis (ie, elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Reporting Requirements

Any potential Hy's Law case should be handled as an SAE and reported promptly to the sponsor.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to >3 x ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study drug.

Regional or country-specific guidelines should be followed. Additional information is provided in the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, 2009.

7.7.1.3. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs is from study Day 1 (predose) through the EOT visit or 30 days after the last study treatment, whichever is later. However, all study protocol-related AEs are to be recorded from the time of informed consent. The reporting period for SAEs is from study Day 1 (predose) through 90 days after the last study treatment, or 30 days following cessation of study treatment if the subject initiates a new anticancer therapy. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

Additionally, beyond the safety reporting period, subjects in disease-progression follow-up after discontinuing study treatment will be assessed at the first follow-up visit for potential irAEs.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

7.7.1.4. Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of an SAE, investigators are to report the event to the sponsor, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Subject number
- Date of event onset
- Description of the event

- Study treatment, if known
- Investigator causality assessment

The completed SAE form is to be emailed or faxed to the sponsor's Drug Safety Department within 24 hours (see email or fax number specified on the SAE report form)

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.7.1.5. Events of Clinical Interest

Selected non-serious and serious AEs are also known as events of clinical interest (ECIs) and must be reported to the sponsor.

ECIs are to be reported to the sponsor irrespective of regulatory seriousness criteria or causality within 24 hours (Section 7.7.1.4).

ECIs for this purpose include:

- An overdose of study product, as defined in Section 5.5.3 (SEA-CD40 and pembrolizumab) that is not associated with clinical symptoms or abnormal laboratory results.
- An elevated AST or ALT lab value that is ≥3 x ULN, and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that is <2 x ULN, as determined by way of protocol-specified laboratory testing, or unscheduled laboratory testing.

ALT and AST criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.7.1.6. Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 7.7.1.4). The sponsor will report all SAEs, including suspected unexpected serious adverse reactions (SUSARs) to regulatory authorities as required per local legislation or regulatory reporting requirements.

7.7.2. Vital Signs

Vital signs measures are to include heart rate, respirations, blood pressure, and temperature. On study treatment dosing days for each study drug, vital signs will be measured and recorded within 30 minutes prior to the start of study drug administration and within 30 minutes after completion of study drug administration. If multiple drugs are being administered on the same day, a single set of vital signs, before the first drug and after the last drug, is acceptable. In the event of an IHR, vital signs will be monitored more frequently as described in Section 5.5.1, Table 11. Vital signs will also be measured at the EOT visits. All vital signs should be measured after the patient has been sitting/resting for at least 5 minutes. If pre- and post-dose measurements overlap with the 30-minute window, only a single set of vital signs is required.

7.7.3. Clinical Laboratory Tests

Samples will be drawn for local labs. Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions. The following laboratory assessments will be performed by local laboratories to evaluate safety at scheduled time points (see Table 1 and Table 2) during the course of the study:

- The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, creatinine, chloride, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, and total bilirubin.
- The CBC with differential is to include the following tests: white blood cell count with differential (including neutrophils, lymphocytes, monocytes), platelet count, Hgb, and hematocrit. Manual differential should be performed if clinically indicated.
- The thyroid panel is to include triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH)
- Hgb A1c

The following laboratory assessment(s) will be performed by local laboratories at scheduled time points (see Table 1 and Table 2) during the course of the study:

- PT/aPTT/INR
- Urinalysis
    - Standard urinalysis including protein, glucose, leukocyte esterase, pH, specific gravity, and blood (with reflexive microscopy, if abnormal)
    - Urine protein and urine creatinine for UPC ratio calculation
    - A serum or urine β-hCG pregnancy test for subjects of childbearing potential

7.7.4. Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Weight will be collected at specified time points (see Section 6) and additionally per institutional standards, if applicable, but does not need to be collected at visits following EOT. Measurements of height obtained within the prior 12 months may be utilized.

7.7.5. Electrocardiograms

All subjects will receive 12-lead ECGs in triplicate at screening and EOT. The first 30 subjects enrolled across Cohorts 1, 2, and 3 at US sites will receive additional ECG monitoring.

Subjects will be monitored for changes in cardiac repolarization through assessment of 12-lead ECGs conducted in triplicate at times outlined in Table 4 and Section 6. ECGs should be performed while the subject is at rest (for at least 10 minutes prior to ECG collection) and prior to obtaining PK and biomarkers samples.

Waiting periods between each ECG are not required. Electronic or paper copies of the tracings may be submitted to the sponsor's designee for possible central assessment.

7.7.6. Pregnancy Testing

For subjects of childbearing potential, a serum or urine β-hCG pregnancy test with sensitivity of at least 25 mIU/mL will be performed at baseline (within 3 days prior to Day 1), within 7 days prior to Day 1 and Day 22 of each 42-day cycle (Cohorts 1, 2, and 3) within 7 days prior to Day 1 of each 21-day cycle (Cohorts 4 and 5), and at the EOT visit (all cohorts). In addition, pregnancy testing will be done once a month for 120 days after the last received dose of study drug for subjects in Cohorts 1, 2, and 3 and once a month for 6 months after the last received dose of study drug for subjects in Cohorts 4 and 5, or per local regulations, where applicable. A negative pregnancy result is required before the subject may receive study drug. Pregnancy tests may also be repeated as requested per institutional review board/independent ethics committee (IRB/IEC) or if required by local regulations.

7.7.7. ECOG Performance Status

ECOG performance Status (Appendix A) will be evaluated at protocol-specific time points. See Table 1, Table 2, and Section 6.

7.8. Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Response will be assessed according to RECIST v1.1, which are standardized criteria for evaluating response in solid tumors. The intervals of evaluation in this protocol are considered appropriate for disease management.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to SEA-CD40. Pharmacokinetic assessments are also common in clinical studies to help characterize dose-exposure-response relationships.

8. DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1. Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of subjects at the site, Seagen or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration, and withdrawal processes
- Current IB/package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- IRB/IEC review and approval process

- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing, and record keeping
- Subject coding and randomization (if applicable)
- Study samples/specimen collection, handling, and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Seagen representative will typically review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study subjects and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by Seagen or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

8.2. Data Management Procedures

Seagen will provide CRF Completion Guidelines for electronic CRF (eCRF) data entry. Study specific data management procedures will be maintained in the data management plan. Queries resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

8.3. Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect subject confidentiality are to be employed during monitoring. The CRFs and related source documents will typically be reviewed in detail by the monitor at each site visit. Original source documents or certified copies are needed for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information collected is correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory authorities and the IRB/IEC.

8.4. Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.

- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.

8.5. Quality Assurance Procedures

The Research and Development Quality group or its designee may conduct audits at the clinical site or other study-related facilities and organizations. Audit reports will be retained by the Research and Development Quality group of Seagen as part of the written record.

8.6. Data Handling and Record Keeping

8.6.1. Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Any change or correction to a CRF will be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The investigator should retain records of the changes and corrections, written and/or electronic.

8.6.2. Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, inpatient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Seagen, whichever is longer. The investigator must contact Seagen prior to destroying any records associated with the study. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to Seagen.

9. DATA ANALYSIS METHODS

9.1. Determination of Sample Size

Up to approximately 200 subjects may be enrolled in this study. This includes up to approximately 40 subjects enrolled in each cohort.

For a sample size of 40 subjects per cohort, assuming confirmed ORR is between 30% and 80%, the 2-sided 95% exact confidence interval (CI) are summarized below:

Confirmed ORR	95% Exact CI (N=40)
30%	(17%, 47%)

Confirmed ORR	95% Exact CI (N=40)
40%	(25%, 57%)
50%	(34%, 66%)
60%	(43%, 75%)
70%	(53%, 83%)
80%	(64%, 91%)

9.2. Study Endpoint Definitions

9.2.1. Confirmed ORR

Confirmed ORR is defined as the proportion of subjects who achieve a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator. Subjects who do not have at least 2 post-baseline response assessments (initial response and confirmation scan) will be counted as non-responders.

9.2.2. Disease Control Rate

Disease control rate (DCR) is defined as the proportion of subjects who achieve a confirmed CR or PR according to RECIST v1.1 as assessed by the investigator or meet the SD criteria at least once after start of study treatment at a minimum interval of 5 weeks. Subjects who do not have at least 1 post-baseline response assessment will be counted as not achieving disease control.

9.2.3. Duration of Response

Duration of response (DOR) is defined as the time from the first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD or death due to any cause, whichever comes first.

DOR data will be censored as described below:

1. Subjects who do not have PD and are still on study at the time of an analysis will be censored at the date of last disease assessment documenting absence of PD.
2. Subjects who started a new anticancer treatment prior to documentation of PD or death will be censored at the date of last disease assessment prior to the start of new treatment.
3. Subjects who are removed from the study prior to documentation of PD will be censored at the date of last disease assessment documenting absence of PD.
4. Subjects with documented PD or death immediately after 2 or more missed disease assessments will be censored at the date of the last disease assessment prior to the missed visits.

DOR will only be calculated for subjects who achieve a confirmed CR or PR as measured by RECIST v1.1 for all tumors.

9.2.4. Progression-Free Survival

PFS is defined as the time from the start of study treatment to the first documentation of PD by RECIST v1.1 or death due to any cause, whichever comes first.

The same censoring rules as outlined in Section 9.2.3 for DOR will be applied to PFS. Subjects lacking an evaluation of tumor response after their first dose of study drug will have their event time censored at Day 1.

9.2.5. Overall Survival

OS is defined as the time from the start of study treatment to date of death due to any cause. In the absence of death, survival time will be censored at the last date the subject is known to be alive (ie, date of last contact).

9.2.6. PRO Endpoints

EORTC QLQ-C30 subscales and NSCLC-SAQ domains and total score will be calculated according to the associated scoring manuals.

9.3. Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters site conduct (eg, adding baseline assessments to define a subgroup). The SAP will be finalized prior to database lock. Any key changes to the methods described in the final SAP will be described in the clinical study report.

9.3.1. General Considerations

In general, descriptive statistics will be presented that include the number of observations, mean, median, standard deviation, minimum and maximum for continuous variables, and the number and percentages per category for categorical variables.

The 2-sided 95% exact CI using Clopper-Pearson method (Clopper 1934) will be calculated for the response rates where applicable (eg, ORR).

For time-to-event endpoints, the median survival time will be estimated using the Kaplan-Meier method; the associated 95% CI will be calculated based on the complementary log-log transformation (Collett 1994).

Safety measurements will be summarized by descriptive statistics based on the safety analysis set. The safety analysis set will include all subjects who received any amount of study treatment.

PRO outcomes endpoints will be summarized using descriptive statistics.

9.3.1.1. Randomization and Blinding

This is a single arm, open-label study. Blinding will not be performed.

9.3.1.2. Adjustments for Covariates

No adjustments for covariates are planned.

9.3.1.3. Handling of Dropouts and Missing Data

Missing data will not be imputed unless otherwise specified. Missing AE start date and/or end date will be imputed while calculating duration of events and treatment-emergent status. Missing subsequent anticancer treatment start date will be imputed while deriving the time-to-event endpoints as applicable. Censoring rules will be applied for the analysis of time-to-event endpoints. Details will be provided in the SAP.

9.3.1.4. Multicenter Studies

No adjustments for multicenter studies are planned.

9.3.1.5. Multiple Comparisons and Multiplicity

No adjustments for multiplicity are planned.

9.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (eg, start date and end date) will be calculated as (end date – start date +1 [in days]) unless otherwise specified in the planned analysis section.

Baseline values used in all statistical analyses will be the most recent non-missing measurement prior to the first dose of study drug unless otherwise specified in the analysis plan.

9.3.1.7. Analysis Sets

The FAS includes all subjects who received any amount of study drug. The PFS and OS analyses will be based on the FAS.

The safety analysis set includes all subjects who received any amount of study drug, and thus is equivalent to the FAS. All safety analyses will be based on the safety analysis set.

The PK analysis set includes all subjects who received any amount of SEA-CD40 and had at least one PK sample.

The response evaluable (RE) analysis set includes all subjects with measurable disease at baseline who received any amount of study drug and had at least 1 postbaseline disease assessment per RECIST v1.1 or discontinued study treatment. The RE will be the primary analysis set for ORR and DCR.

The PRO analysis set includes all subjects who received any amount of study drug and have at least one PRO assessment. All PRO analyses will be based on the PRO analysis set.

Additional analysis sets of subjects may be defined in the SAP.

9.3.1.8. Examination of Subgroups

As exploratory analyses, subgroup analyses may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.9. Timing of Analyses

The primary analysis will be conducted when all treated subjects in a cohort have been followed for at least 6 months or come off study, whichever comes first. Subsequent data cutoff dates may be defined to allow for more precise estimates of time-to-event endpoints.

Interim analysis for futility will be performed separately for each cohort after approximately 15 subjects of a given cohort have been treated and are response evaluable post-baseline.

9.3.2. Subject Disposition

An accounting of study subjects by disposition will be tabulated and the number of subjects in each analysis set will be summarized. Subjects who discontinue study treatment and subjects who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.3.3. Subject Characteristics

Demographics and other baseline characteristics will be summarized by cohort for the FAS. Details will be provided in the SAP.

9.3.4. Treatment Administration

Treatment administration will be summarized by cohort for the safety analysis set. Summary statistics for duration of therapy, number of cycles per subject, and the number and percentage of subjects treated at each cycle will be presented. Details will be provided in the SAP.

9.3.5. Efficacy Analyses

The primary analysis of ORR and DCR will be based on the RE analysis set. Exploratory analyses of ORR based on the FAS will also be performed. The primary analysis of PFS and OS will be based on the FAS.

9.3.5.1. Primary Efficacy Analyses

The primary endpoint of this study for all tumor types is the confirmed ORR per investigator assessment. The ORR is defined as the proportion of subjects who achieve a confirmed CR or PR according to RECIST v1.1. The ORR of each cohort and its exact 2-sided 95% CI using the Clopper-Pearson method (Clopper 1934) will be calculated.

9.3.5.2. Secondary Efficacy Analyses

The DCR will be estimated for each cohort and the 95% CIs will be calculated using the Clopper-Pearson method.

The DOR, PFS, and OS for each cohort will be estimated using the Kaplan-Meier methodology, and the medians and associated 95% CIs will be calculated. Kaplan-Meier plots will be provided as appropriate.

9.3.6. Pharmacokinetic and Immunogenicity Analyses

SEA-CD40 concentrations will be summarized with descriptive statistics at each PK sampling time point. Selected PK parameters will be estimated by noncompartmental analysis and summarized using descriptive statistics.

The incidence of ADA will be summarized using the safety analysis set.

9.3.7. Biomarker Analyses

Relationships of biomarker parameters (eg, baseline values, absolute and relative changes from baseline) to efficacy, safety, and PK parameters may be explored. Relationships and associated data that are determined to be of interest may be summarized. Details will be described separately in the SAP or biomarker analysis plan.

9.3.8. Patient-Reported Outcomes Analyses

PRO assessments will be analyzed to determine if treatment affects PRO scores. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data will be provided at each scheduled assessment time point. Further analyses, if planned, will be provided in the SAP.

Summary statistics of actual and change from baseline of EORTC QLQ-C30 subscales for all cohorts and NSCLC-SAQ domains and total scores for Cohorts 4 and 5 at each scheduled visit will be provided. Number and frequency of PGI-S and PGI-C responses in Cohorts 4 and 5 will be presented at each scheduled visit.

Time-to-deterioration (TTD) for the NSCLC-SAQ questionnaire is defined as the time from baseline (Cycle 1 Day 1) until the first change from baseline that is less or equal to the minimal clinically important difference and that was maintained for 2 or more consecutive assessments. Details on the calculation of the MCID will be provided in the SAP.

The TTD analyses will be performed using the Kaplan-Meier method and will include the subjects without a missing baseline score. Median TTD and 95% CI will be provided, if feasible.

9.3.9. Safety Analyses

All safety analyses will be performed by cohort and overall using the safety analysis set.

9.3.9.1. Extent of Exposure

Duration of treatment, number of cycles, total dose, and dose intensity will be summarized. Dose modifications, including dose delay, dose reduction, and unplanned dose adjustment, will be summarized. Details will be provided in the SAP.

9.3.9.2. Adverse Events

An overview of AEs will provide a tabulation of the incidence of all AEs, treatment-emergent AEs, treatment-related AEs, Grade 3 and higher treatment-emergent adverse events (TEAEs), SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will be defined as treatment-emergent if they are newly occurring or worsen following study treatment.

TEAEs will be listed and summarized by Medical Dictionary for Regulatory Activities (MedDRA), preferred term, severity, and relationship to SEA-CD40. In the event of multiple occurrences of the same AE with the same preferred term in 1 subject, the AE will be counted once as the occurrence. AEs leading to premature discontinuation of SEA-CD40 will be summarized and listed in the same manner.

9.3.9.3. Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.9.4. Clinical Laboratory Results

Summary statistics of laboratory results and changes from baseline will be tabulated by scheduled visit. Grading of laboratory values will be assigned programmatically per the NCI CTCAE v5.0. Shift tables comparing the worst post-baseline to baseline CTCAE grade will be presented. Laboratory values will be listed with grade per CTCAE and flagged when values are outside the normal reference range.

9.3.9.5. Other Safety Analyses

Vital Signs

Vital signs data will be listed. Summary statistics of vital signs and change from baseline may be tabulated where appropriate.

ECOG Performance Status

ECOG performance status will be summarized for each scheduled visit. Shifts from baseline to the best and worst postbaseline score may be tabulated.

ECG

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) may be summarized for each scheduled ECG and shifts from baseline may be tabulated.

9.3.10. Interim Analyses

Interim efficacy analyses will be performed separately for each cohort after approximately 15 subjects of a given cohort have been treated and are response evaluable post-baseline. The Bayesian PpoS approach will be used to determine the criteria for continuation (see Appendix E). A cohort is considered "successful" if the 90% CI of the response rate at the maximum sample size excludes the background rate. At the time of each interim analysis, the PpoS will be calculated. A PpoS <5% indicates that it is unlikely the ORR will be better than the response rate of current standard of care at the end of the cohort given the interim result. Based on efficacy and safety data, together with the PpoS, a cohort may be stopped early by the sponsor. A cohort may also be discontinued at any point at the discretion of the sponsor. The details of the PpoS method are provided in Appendix E.

The predictive probability method allows the PpoS be computed at any interim time and provides flexibility in monitoring treatment activity continuously after the initial interim analysis.

10. INFORMED CONSENT, ETHICAL REVIEW, AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Note for Guidance on Good Clinical Practice (ICH Harmonised Tripartite Guideline E6 (R2); FDA CFR [21 CFR § 50, 56, 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1. Informed Consent

The investigator is responsible for presenting the risks and benefits of study participation to the subject in simple terms using the IRB/IEC approved informed consent document and for ensuring subjects are re-consented when the informed consent document is updated during the study, if required. The investigator will ensure that written informed consent is obtained from each subject, or legally acceptable representative, if applicable to this study, by obtaining the signature and date on the informed consent document prior to the performance of protocol evaluations or procedures.

10.2. Ethical Review

The investigator will provide the sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the informed consent document before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee are provided in the investigator file.

The investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- Informed consent document and updates
- Clinical IB and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The investigator must provide the following documentation to the sponsor or its designee:

- The IRB/IEC periodic (eg, quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the informed consent document.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

10.3. Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.3.1. Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file.

10.3.2. Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study subject) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.4. Study Documentation, Privacy and Records Retention

To protect the safety of subjects in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents or certified copies.

Records containing subject medical information must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject authorization contained in the informed consent document for the study (the Authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of subject identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

10.5. Clinical Trial Agreement

Payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the clinical trial agreement.

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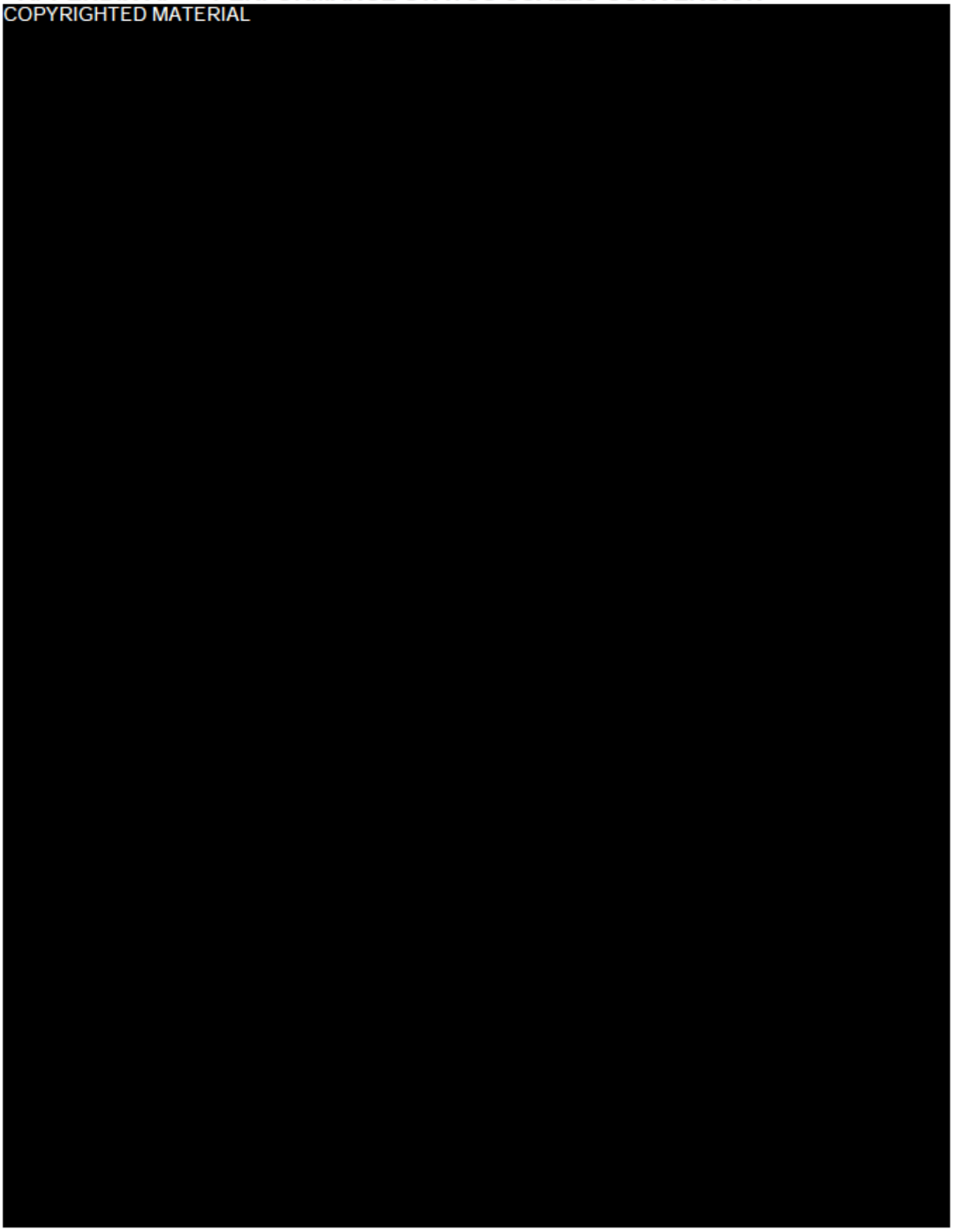
APPENDIX A. PERFORMANCE STATUS SCALES CONVERSION



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APPENDIX B. CONTRACEPTIVE AND BARRIER GUIDANCE

Definitions of Reproductive Potential

A person of childbearing potential is anyone who has experienced menarche and who has not undergone permanent sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person over age 45 in the absence of other biological, physiological, or pharmacological causes.

A subject who can get someone pregnant is anyone who has testes and who has not undergone permanent sterilization (defined as bilateral orchidectomy).

Birth Control/Contraceptive Guidance

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is a highly effective method of birth control (contraception). Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (see Section 4.1).

Acceptable Effective Methods of Birth Control (Contraception)

Subjects who are of childbearing potential or whose partners are of childbearing potential, and who are sexually active in a way that could lead to pregnancy must choose TWO of the following acceptable methods of birth control (contraception), at least ONE of which must be highly effective:

Highly Effective Methods of Birth Control	Effective Methods of Birth Control
Abstinence (as defined above).	Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
Combined (estrogen and progestogen containing) oral, intravaginal, or transdermal hormonal contraception with inhibition of ovulation.	Male or female condom with or without spermicide.
Oral, implantable, or injectable progestogen-only hormonal contraception associated with inhibition of ovulation.	Cap, diaphragm, or sponge with spermicide.
Intrauterine hormone-releasing system.	A combination of a male condom with either a cap, diaphragm, or sponge with spermicide (double barrier).
Intrauterine device with failure rate <1%.	
Bilateral tubal occlusion/ligation.	
Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia).	

The following methods of birth control (contraception) are not considered acceptable or effective

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only

- Lactational amenorrhea method (LAM)

Acceptable methods for preventing secondary exposure to seminal fluid

Subjects born male and who are sexually active with a pregnant person must use a male condom (even if the subject has had a vasectomy).

Subjects born male and who are sexually active with a breastfeeding person must use a male condom (even if the subject has had a vasectomy). In addition, it is recommended that the breastfeeding partner use a highly effective female contraceptive method as listed in section "Acceptable Effective Methods of Birth Control (Contraception)".

APPENDIX C. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION OF HEART FAILURE

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APPENDIX D. IMMUNE-BASED RESPONSE EVALUATION CRITERIA FOR SOLID TUMORS AND RECIST VERSION 1.1

Response Evaluation Criteria for Solid Tumors (RECIST) Version 1.1 (Eisenhauer 2009)		Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST) (Seymour 2017)	
Term	Definition	Term	Definition
Complete response (CR)	• Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm • Cannot have previously met criteria for PD • Confirmation required only for non-randomized studies	iCR (both target and non-target lesions)	• Defined per RECIST 1.1 criteria • Can be assigned following iUPD (but not iCPD) • Confirmation per RECIST 1.1
Partial response (PR)	• A ≥30% decrease in the sum of diameters of target lesions (longest for non-nodal target lesions and the short axes for nodal target lesions), taking as reference the baseline sum diameters • Cannot have previously met criteria for PD • Confirmation required only for non-randomized studies	iPR (target lesions only)	• Defined per RECIST 1.1 criteria • Can be assigned following iUPD (but not iCPD) • Confirmation per RECIST 1.1
Stable disease (SD)	• Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study • Cannot have previously met criteria for PD • Confirmation is not required	iSD (target lesions only)	• Defined per RECIST 1.1 criteria • Can be assigned following iUPD (but not iCPD) • Confirmation per RECIST 1.1

Response Evaluation Criteria for Solid Tumors (RECIST) Version 1.1 (Eisenhauer 2009)		Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST) (Seymour 2017)	
Term	Definition	Term	Definition
	—	Non-iCR/ non-iUPD (non-target lesions only)	• Neither CR nor PD criteria met per RECIST 1.1 • Can be assigned following iUPD (but not iCPD) • Overall response assigned based on target lesions
Progressive disease (PD)	• A ≥20% relative increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (including baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase ≥5 mm • The appearance of 1 or more new lesions is also considered progression • Confirmation is not required unless equivocal	Unconfirmed PD (iUPD) (both target and non-target lesions)	• Progression defined per RECIST 1.1 criteria • Confirmation of progression is required • Progression confirmed by (1) further increase in size or number of new lesions in category (ie, target or non-target) in which progression was first identified OR (2) progression per RECIST 1.1 in lesion categories that had not previously met PD criteria • If progression is not confirmed AND tumor shrinkage occurs compared to baseline (ie, iCR, iPR, or iSD criteria met), the status is reset and iUPD must occur again (compared to nadir values) and be confirmed by further growth at next assessment for iCPD to be assigned • If progression is not confirmed AND no change in tumor size or extent from iUPD occurs, then response would again be iUPD • iUPD can be assigned multiple times as long as iCPD is not confirmed at next assessment

Response Evaluation Criteria for Solid Tumors (RECIST) Version 1.1 (Eisenhauer 2009)		Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST) (Seymour 2017)	
Term	Definition	Term	Definition
	—	Confirmed PD (iCPD) (both target and non-target lesions)	• Progression confirmed as described for iUPD • Criteria for iCPD (after iUPD) are NOT met if CR, PR, or SD occur at assessment following iUPD; the status is reset
New measurable or non-measurable lesions	• Always represent PD	New target or non-target lesions	• Result in assignment of iUPD • For new lesions, iCPD is only assigned if at next assessment (1) additional new lesions appear OR (2) increased size of new lesions is seen (≥5 mm for sum of new target lesion, or any increase in new non-target lesion) OR (3) new lesions appear when none were previously recorded
Non-target lesions	• Changes contribute to defining CR, PR, SD, and PD	Non-target lesions	• Changes contribute to defining CR, non-iCR/non-iCPD, iUPD, and iCPD

CR=complete response; iCPD=immune confirmed progressive disease; iCR=immune complete response; iPR=immune partial response (target lesions only); iSD=immune stable disease (target lesions only); iUPD=immune unconfirmed progressive disease; non-iCR/non-iUPD=neither CR nor PD (non-target lesions only); PD=progressive disease; PR=partial response; SD=stable disease.

APPENDIX E. INTERIM ANALYSIS USING PREDICTIVE PROBABILITY OF SUCCESS

Interim evaluation of efficacy will be performed separately for each cohort after approximately 15 subjects of a given cohort have been treated and had at least one response assessment post-baseline. The Bayesian predictive probability of success (PPoS) method (Lee 2008a) will be used to determine the continuation criteria. PPoS is the probability of achieving "success" should the cohort be continued to the maximum sample size of 40 given the data observed at interim, and a cohort is considered "successful" if the 90% confidence interval (CI) of the response rate at the maximum sample size excludes the background rate.

Using the PD-(L)1-naive melanoma cohort (Cohort 3) as an example, the PPoS is computed as follows:

1. Let N_{max}=40 be the maximum sample size of a cohort, and n=15 be the number of subjects treated and evaluated for the response status at the time of interim evaluation.
2. Assume the prior distribution of the response rate p follows a beta distribution

   $p \sim \text{beta}(a_0, b_0)$, with $a_0 = 0.41$ and $b_0 = 0.59$ to reflect a prior belief that the response rate for the study treatment is halfway between the background rate p_0=33% and the estimated response rate that is 15% higher (48%).
3. Let X be the number of responders in the first n subjects, and X follows a binomial distribution $X \sim \text{binomial}(n, p)$. The likelihood function for the observed data x is

   $L(p \mid X = x) \propto p^x (1-p)^{n-x}$
4. The posterior distribution of the response rate given $X = x$ follows a beta distribution

   $p \mid x \sim beta(a_0 + x, b_0 + n - x)$
5. Let Y be the number of responders in the potential m future subjects, where $m = (N_{max} - n)$, thus Y follows a beta-binomial distribution, $Y \sim$ beta-binomial$(m, a0 + x, b0 + n - x)$.

   Given $Y = i$, the posterior distribution of p follows beta $(a_0 + x + i, b_0 + N_{max} - x - i)$.
6. Let CI_l be the 90% exact CI of the response rate p using the Clopper-Pearson method, given x responders in the first n subjects and i responders in the m future subjects.
7. Compute $PPoS = \sum_{i=0}^{m} \{\Pr(Y = i \mid x) \times I(CI_l > p_0)\}$.
   - If PPoS >0.05, then the cohort will continue. If PPoS <0.05, then the sponsor in consultation with the SMC may decide to stop further enrollment in the cohort after careful assessments of the totality of data.

The estimated PPoS based on number of responders observed among the first 15 subjects are presented in Table 1. Operating characteristics are presented in Table 2.

Table 1: Estimated PPoS Based on Number of Responders Among the First 15 Subjects

Number of responders among first 15 subjects	Cohorts 1 and 2 (p_0=4%)	Cohort 3 (p_0=33%)	Cohort 4 (p_0=49%)	Cohort 5 (p_0=32%)
0	0.0044	0.0000	0.0000	0.0000
1	0.1631	0.0000	0.0000	0.0000
2	0.5467	0.0003	0.0000	0.0003
3	0.8743	0.0037	0.0000	0.0037
4	0.9870	0.0236	0.0001	0.0234
5	1.0000	0.0951	0.0010	0.0944
6	1.0000	0.2583	0.0084	0.2570
7	1.0000	0.5025	0.0439	0.5009
8	1.0000	0.7452	0.1509	0.7439
9	1.0000	0.9058	0.3599	0.9051
10	1.0000	0.9760	0.6250	0.9758

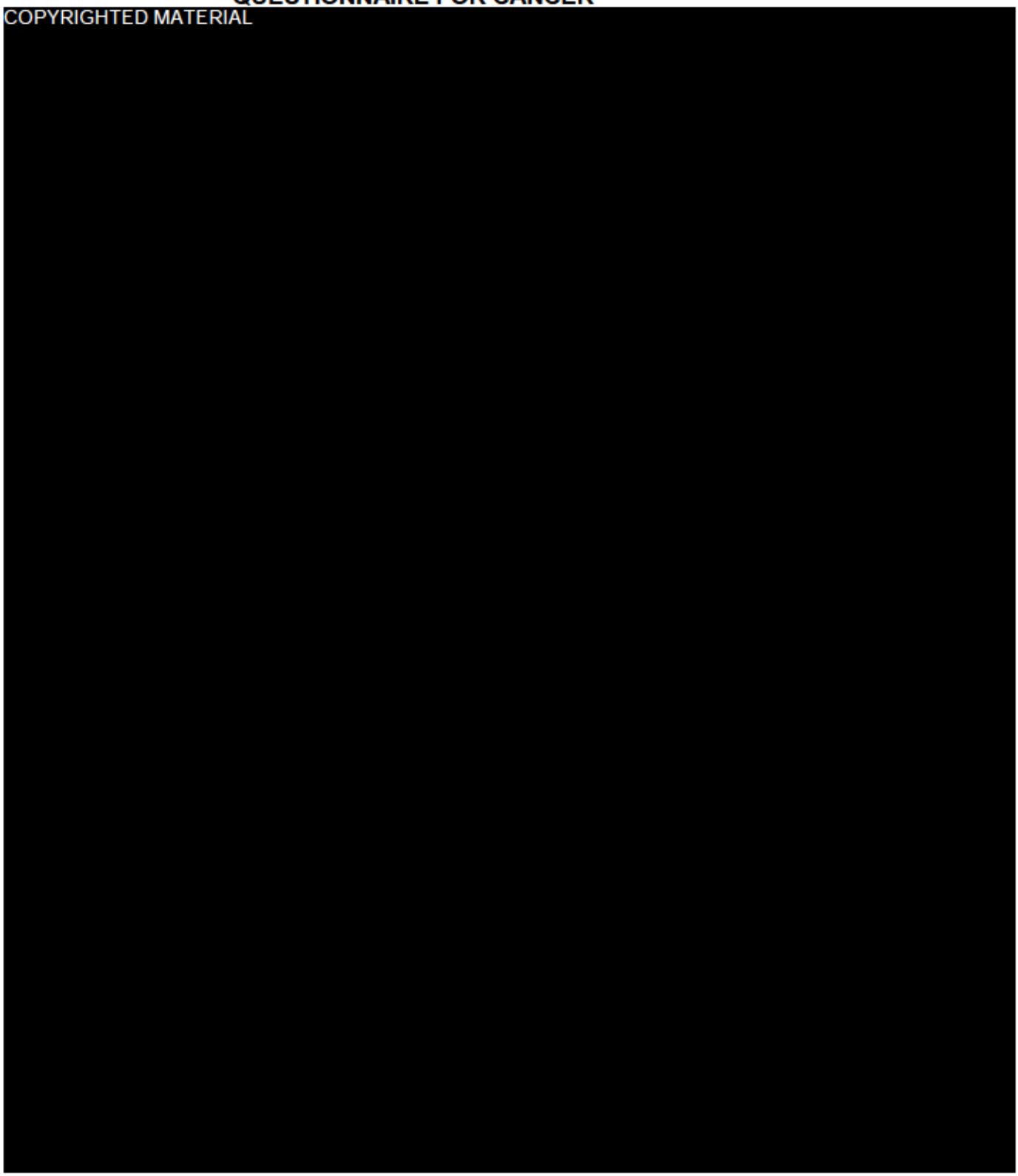
The prior distribution is assumed to be beta (0.12, 0.88), beta (0.41, 0.59), beta (0.57, 0.43), and beta (0.4,0.6), respectively, to approximate the background rate in each disease cohort.
The background rate in Cohort 1 is assumed to be 4% based on (Hamid 2017)
The background rate in Cohort 2 is assumed to be 4% based on (Algazi 2016) and (Heppt 2017)
The background rate in Cohort 3 is assumed to be 33% based on (Robert 2015)
The background rate in Cohort 4 is assumed to be 49% based on (Gadgeel 2020)
The background rate in Cohort 5 is assumed to be 32% based on (Gadgeel 2020)

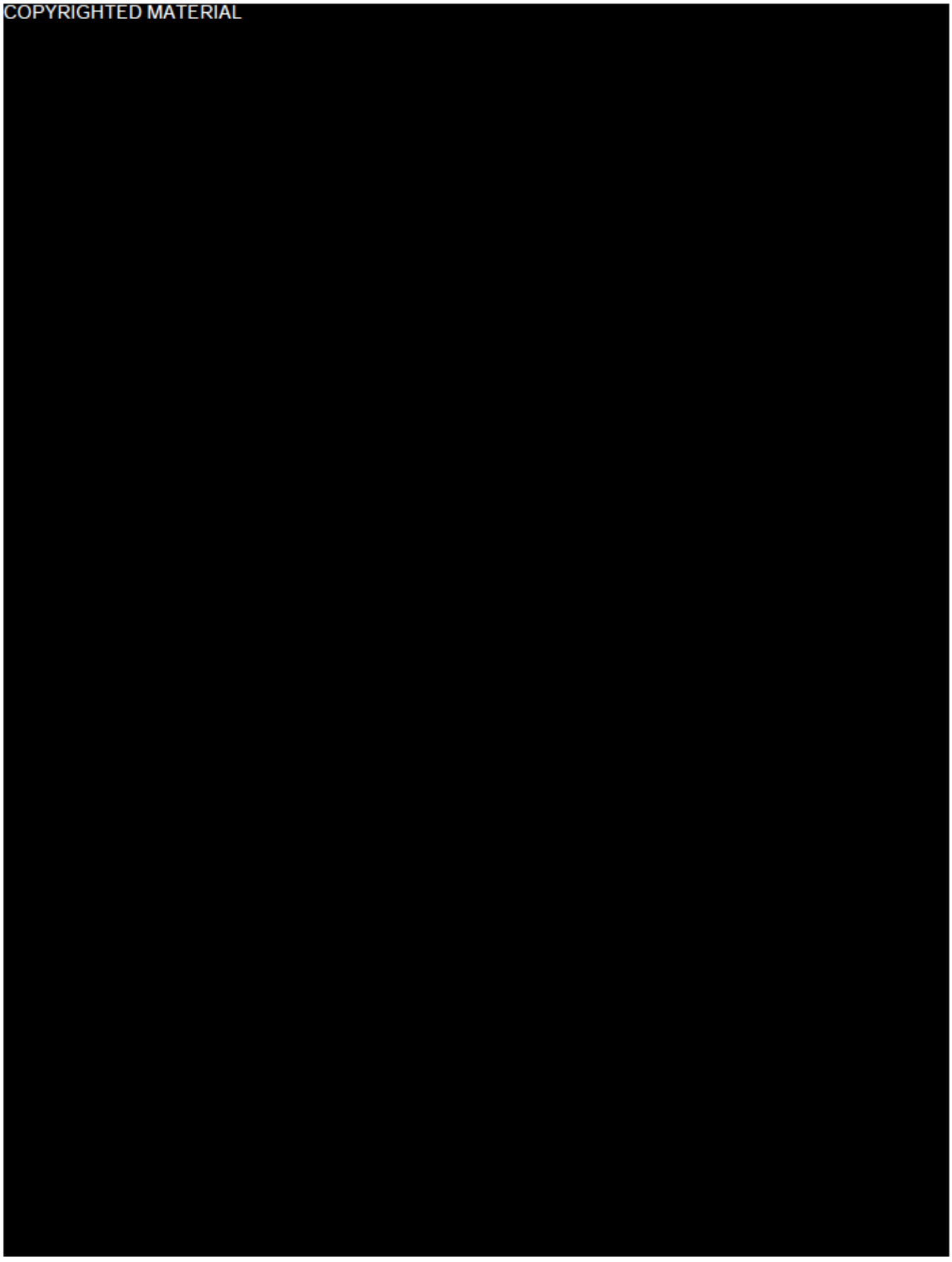
Table 2: Operating Characteristics

Background rate (p_0)	Scenario	True response rate	Probability of futility stopping	Probability of success	Average number of subjects
4%	1	5%	0.4633	0.0480	28.4
	2	10%	0.2059	0.3710	34.9
	3	15%	0.0874	0.7367	37.8
	4	20%	0.0352	0.9241	39.1
	5	25%	0.0134	0.9840	39.7
33%	1	10%	0.9873	0.0000	15.3
	2	20%	0.8358	0.0001	19.1
	3	30%	0.5155	0.0148	27.1
	4	40%	0.2173	0.2089	34.6
	5	50%	0.0592	0.6821	38.5
49%	1	30%	0.9500	0.0000	16.3
	2	40%	0.7869	0.0012	20.3
	3	50%	0.5000	0.0403	27.5
	4	60%	0.2131	0.3174	34.7
	5	70%	0.0500	0.8074	38.7
32%	1	10%	0.9873	0.0000	15.3
	2	20%	0.8358	0.0001	19.1
	3	30%	0.5155	0.0148	27.1
	4	40%	0.2173	0.2089	34.6
	5	50%	0.0592	0.6821	38.5

The prior distribution is assumed to be beta (0.12, 0.88), beta (0.41, 0.59), beta (0.57, 0.43), and beta (0.4, 0.6), respectively, to approximate the background rate in each disease cohort. A cohort is considered "successful" if the 90% CI of the response rate at the maximum sample size excludes the background rate.

APPENDIX F. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER (EORTC) QUALITY-OF-LIFE QUESTIONNAIRE FOR CANCER





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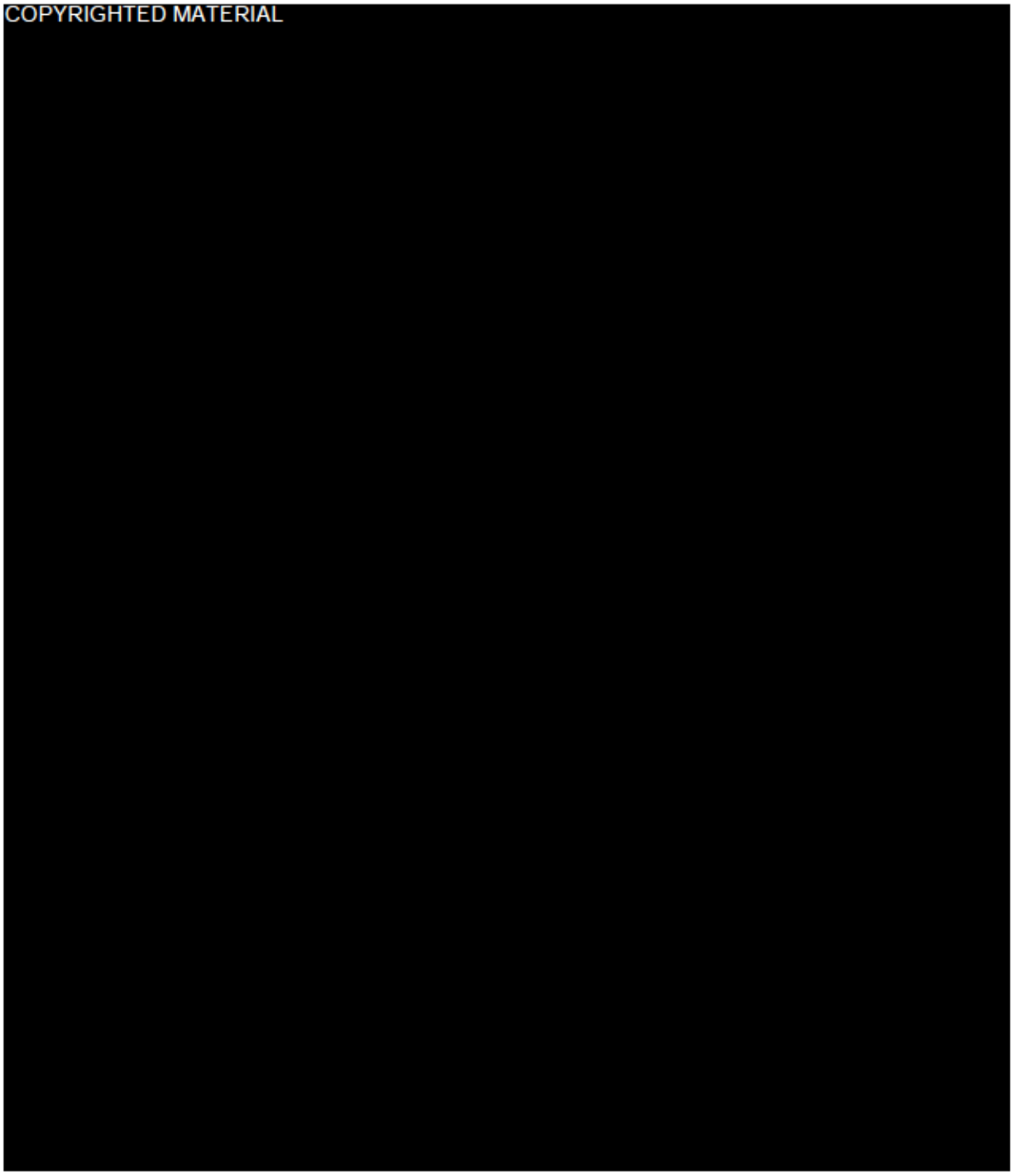
APPENDIX G. NON-SMALL CELL LUNG CANCER SYMPTOM ASSESSMENT QUESTIONNAIRE (NSCLC-SAQ) V1.0



Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) Version 1.0

Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) v1.0

Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) Version 1.0

APPENDIX H. PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS) SCALE

Please choose the response below that best describes the severity of your lung cancer symptoms over the past week.

0 ☐ None

1 ☐ Mild

2 ☐ Moderate

3 ☐ Severe

4 ☐ Very severe

APPENDIX I. PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE

Please choose the response below that best describes the overall change in your lung cancer symptoms since you started taking the study medication.

1 ☐ Much better

2 ☐ A little better

3 ☐ No change

4 ☐ A little worse

5 ☐ Much worse

APPENDIX J. INVESTIGATOR SIGNATURE PAGE

Investigator Statement and Signature

I have read the attached protocol entitled "An Open-label, Phase 2 Basket Study of SEA-CD40 Combination Therapies in Advanced Malignancies"

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature	Date
Investigator Name, Printed	

APPENDIX K. DOCUMENT HISTORY

Version	Date
Original	06-May-2021
Global Amendment 1	10-Jun-2021
Global Amendment 2	04-Apr-2022
Global Amendment 3	05-Apr-2023

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
5.2.2	Add SEA-CD40 infusion rate and a post-dose observation period after the first infusion	Include relevant information from the Pharmacy Instructions in the protocol for clarity
5.2.3	Add additional guidance for AEs requiring SEA-CD40 discontinuation	Clarification
6.3.3.2	Add observation period following SEA-CD40 infusion	Clarification
7.7.1.3	Changed reporting period for all SAEs to 90 days post-last dose	Standardize SAE reporting timeline for all study drugs

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Synopsis; Table 1, Table 2, and Table 3; Sections 3.1.1 and 4.1	Inclusion criterion 1.a.vi has been added to indicate that subjects in France will not be enrolled in Cohort 1.	There is a different standard of care in France.
Synopsis; Table 1, Table 3, and Table 7; Sections 6.2.3.4 and 7.7.6	For Cohorts 1, 2, and 3 the second dose per cycle and all accompanying evaluations will be done on Day 22 (not Day 21)	To correct error.
Synopsis; Section 4.1	Inclusion criteria 1.a.v has been added so that subjects in Cohort 1 with a targetable BRAF mutation must have been treated with, been intolerant of, or declined treatment with BRAF/MEK targeted therapy prior to study entry.	To allow investigators to determine, in partnership with the subjects whether BRAF/MEK should be administered prior to the study versus reserving this treatment for a subsequent line of therapy.
Synopsis; Section 3.1.3	The length of study treatment for subjects who achieve stable disease has been changed from "2 years" to "approximately 2 years".	To allow subjects to discontinue treatment at the end of a cycle.

Section(s)	Change	Rationale
Table 1	A footnote (I) has been added to indicate the window for collection of laboratory samples is 3 days on Day 8	Correction of omission.
Table 1 and Table 2	A window of (±1 week) has been added for CT scans completed after the first 24 weeks.	Correction of omission.
Table 1 and Table 2; Section 5.8	New Section 5.8 added to allow subjects who discontinue 1 component of a combination therapy but continue on another component to skip or move study visit assessments on days when the discontinued component would have been administered.	To reduce subject visit burden in the event of discontinuation of a single treatment.
Table 1 and Table 2; Section 6.1	The assessment "urinalysis" has been changed to "urinalysis, including UPC ratio."	Clarification.
Table 1 and Table 2; Sections 6.5 and 7.7.6	Pregnancy test after the last dose of study drug will be performed monthly *or per local regulations*.	Clarification.
Table 1 and Table 2; Sections 6.5 and 7.7.1.3	Chemistry and thyroid panels have been added to assessments required for the first follow-up visit. Text has been updated/added to collect SAEs for 90 days after the last study treatment and irAEs will be collected through the first follow-up visit. If a subject starts a new anticancer therapy, collection of SAEs that are not related to study treatment and irAEs may be stopped 30 days after the cessation of study treatment. Study treatment-related SAEs that occur after the safety reporting period should also be reported to the sponsor.	To further ensure subject safety by extending the time to collect immune-related AEs.
Table 1 and Table 2; Section 6.6	The timing of the first survival follow-up visit has been changed from 1 month to 12 weeks (±1 week) after the last radiographic scan that demonstrates disease progression or from initiation of a new anticancer treatment. The timing of subsequent survival follow-up visit has been changed from monthly to every 12 weeks (±1 week).	To reduce subject burden.
Table 3 and Table 5	The window for all predose samples has been changed from "–4 hours" to "within 4 hours prior to". Footnote placement and numbering has been modified.	Clarification.

Section(s)	Change	Rationale
Table 3 and Table 5	A note has been added to indicate that if collection kits are not available on the intended collection day, the sample may be omitted in consultation with the sponsor.	To allow for missed assessments based on kit supply.
Table 3	The Day 1 end of infusion window for PK sample collection has been increased from 15 minutes to 30 minutes.	To allow sufficient time for the end of infusion ECG.
Section 4.1	Inclusion criterion 1.a.ii has been modified to indicate that prior adjuvant/neoadjuvant immunotherapy may not count as a line of prior therapy.	Clarification.
Section 4.1	Inclusion Criteria 1.a.iv and 1.b.iii have been modified to indicate that, for subjects entered into the study after enrollment for the interim analysis is completed, fresh biopsy sampling is preferred; however, an archival sample may be substituted for a fresh baseline sample if it is in the subject's best interest.	Clarification.
Section 4.1	The following has been added to inclusion criterion 1.c.ii: Subjects with a targetable BRAF mutation who are rapidly progressing should be treated with BRAF/MEK targeted therapy to stabilize disease prior to study entry, unless contraindicated.	To align with international standard of care.
Section 4.1	Inclusion criterion 2 has been modified to allow a fresh tumor biopsy at baseline if archival tissue is not available.	To allow fresh tumor biopsy at baseline and align this criterion with criteria 1.a.iv and 1.b.iii and with Section 7.4.
Section 4.1	Inclusion criterion 6 has been modified to require an ANC ≥2000 µL for subjects in Cohorts 4 and 5.	To align with requirement for similar agents when used in NSCLC.
Section 4.2	Exclusion criterion 15 has been deleted.	This criterion is already covered in greater detail in Inclusion criterion 7.
Sections 4.2, 5.3, and 5.4.3; Table 8	For Cohorts 4 and 5, the following prohibited concomitant medications have been added: • Yellow fever vaccines. • Ibuprofen or other non-steroidal anti-inflammatory drugs (NSAIDs) (including premedication) in patients with CrCl <80 mL/min, during the	For consistency with current pemetrexed and carboplatin Summaries of Product Characteristics (SmPCs).

Section(s)	Change	Rationale
	32 days before, the day of, and 2 days after pemetrexed administration. • Long acting NSAIDs (such as piroxicam or rofecoxib) for 5 days before, the day of, and 2 days after pemetrexed administration.	
Section 5	Section reconfigured to clarify dose modifications	Clarification.
Section 5.1.1.2	The reference to overall SEA-CD40 infusion duration of up to 10 hours has been deleted.	To correct inconsistency with the pharmacy manual.
Section 5.1.1.2	The term "cycles" has been changed to "doses."	To correct error as some regimens include more than 1 dose in a cycle.
Section 5.1.3.2	Source for pemetrexed and carboplatin specified by country.	Clarification.
Section 5.1.3.3	Text modified to indicate that CrCl should be calculated using the Cockcroft-Gault equation.	To correct error.
Section 5.2.1 and Table 7	The dose modification and toxicity management for irAEs have been updated to include that such toxicity may be associated with pembrolizumab and/or SEA-CD40.	Clarification.
Section 5.3	Corticosteroid premedication for pemetrexed dose has been changed from 20 mg to 10 to 20 mg.	To allow flexibility in prophylaxis dosing.
Section 5.3	Text has been modified to indicate the suggested antiemetic therapy applies to NSCLC subjects during the first 4 weeks of treatment with carboplatin.	Clarification.
Sections 5.3 and 5.4.3	Added text to clarify that immunosuppressive medications, such as steroids, may not be used as prophylaxis for IRRs on days where SEA-CD40 is administered.	Clarification.
Section 5.4.2	Added that use of bone modifying agents, when applicable, is allowed.	Clarification.
Section 5.5.4	New section added for management of ocular events.	Subject safety.

Section(s)	Change	Rationale
Section 5.7	New section added outlining conditions for continued access to study drug after the end of the study.	To allow for continued access to study drug for subjects who are benefiting from treatment.
Section 6.2.1	Text added to allow procedures conducted as part of a subject's routine clinical management and before execution of informed consent may be used for screening or baseline purposes.	To reduce subject burden.
Section 6.2.1	Text added to allow subjects to be rescreened once.	To allow rescreening.
Sections 6.2.1, 6.2.3, 6.3.1, 6.3.2, 6.3.3, and 6.4	Each section has modified to clarify that PRO assessments will be collected for subjects entered in the study after enrollment for the interim analysis has been completed.	Clarification and to make these sections consistent with the Schedule of Events and Section 6
Section 6.2.3.3, 6.2.3.4, 6.3.3.1, 6.3.3.2, and 7.7.2	Pre- and post-dose vital signs and/or windows added/updated as appropriate	To correct omission and ensure consistency.
Section 6.5	CT/MRI scan language has been modified to indicate scans of the chest, abdomen, and pelvis are required for Cohorts 1–3 and scans of the chest and abdomen are required for Cohorts 4 and 5.	To correct error and make text consistent with the respective Schedules of Events.
Section 7.2	Text has been updated to indicate that copies of tumor images will be forwarded to the sponsor/designee per the instructions in the central imaging manual.	Clarification.
Section 7.7.1.2	Changed the pregnancy reporting timeline from within 48 hours to within 24 hours of becoming aware of a pregnancy.	Subject safety.
Section 7.7.3	HbA1c has been added to the list of laboratory tests.	To make consistent with the Schedule of Events and Section 6.
Section 7.7.3	Added that standard urinalysis includes protein, glucose, leukocyte esterase, pH, specific gravity, and blood. Glucose has been added to the list of tests in the chemistry panel	Clarification.
Section 7.7.6	Added that pregnancy testing will be done once a month for 120 days after the last dose of study drug for subjects in Cohorts 1, 2, and 3 and once a month for 6 months after the last dose of study drug for subjects in Cohorts 4 and 5, or per local regulations, where applicable	To make consistent with pregnancy testing requirements in the Sections 4 and 6.5.

Section(s)	Change	Rationale
Section 9.3.1.7	Text has been updated to indicate that the analyses of PFS and OS will be based on the FAS.	To better analyze the response endpoints.
Section 9.3.1.7 and throughout document as applicable	The "efficacy evaluable" analysis set has been changed to "response evaluable" analysis set and defined as all subjects with measurable disease at baseline who received any amount of study drug and had at least 1 postbaseline disease assessment per RECIST v1.1 or discontinued study treatment. The RE will be the primary analysis set for ORR and DCR.	To better analyze the response endpoints.
Section 9.3.5	Section has been updated to indicate than an exploratory analyses of ORR based on the FAS will also be performed. The primary endpoint has been modified to indicate it will be evaluated in the RE analysis set.	To better define efficacy.
Section 9.3.10	A reference to Appendix E has been added.	To direct the reader to additional information.

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Protocol Synopsis; SOE table; Section 6.1; Section 6.2; Section 7.2; Section 7.3; Section 7.4; Section 7.6 and throughout document as applicable	The following text was added: **Biomarker assessments may be discontinued at any point at the sponsors discretion.** **PRO collections may be discontinued at the discretion of sponsor.** **Note: Any samples and data collection for the exploratory objectives which are not necessary to evaluate any primary/secondary objectives can be discontinued at the discretion of the sponsor (for example, but not limited to: PROs, SEA-CD40 PK, CD40 ADA, Plasma, PD flow, Tumor biopsy, Genotyping, Serum, PBMC, cfDNA).**	To allow flexibility in data collection of exploratory objectives to reduce trial burden.
Section 1.6	Text updated to add data from repeat-dose study in cynomolgus monkeys at 30 mg/kg dose.	Added new nonclinical safety information.
Section 2	The following revisions were made:	Correction

	To characterize the pharmacokinetics (PK) of SEA-CD40 and ~~pembrolizumab and~~ incidence of antidrug antibodies (ADAs) when SEA-CD40 is administered in combination with other therapies	
Section 3.1.5	**The following revisions were made:** **If the sponsor terminates the study early, investigators are instructed to continue disease assessments per protocol, unless otherwise indicated by the sponsor, until the study termination date. Subjects discontinuing treatment will be followed for 30 days post-treatment for SEA-CD40 and/or chemotherapy and 90 days post-treatment for pembrolizumab, unless safety concerns warrant further follow-up. Patients in survival follow-up at the time of early study termination will be contacted one last time, regardless of the date of the prior assessment, for final survival assessment. The investigator will be expected to monitor for and report any SAEs and pregnancies, as detailed in Section 7.7.1.3 and Section 7.7.6. Truncated data may be collected at the discretion of the sponsor.**	Provide more flexibility to study sites for the treatment and management of subjects in the study.
Section 3.1.8	The following text was added: **Trial Operations and Data Collection after SEA-CD40 expiry** **If at least 6 months has elapsed since the last subject was enrolled in the study, and if there are no more than 15 subjects still on study receiving only drug(s) with a known safety profile (such as pembrolizumab/pemetrexed combination therapy or pembrolizumab monotherapy), a database lock of the study may occur to allow the analysis of the SEA-CD40-related study data.** **Any remaining subjects may continue to receive study treatments other than SEA-CD40 (pembrolizumab with or without carboplatin and pemetrexed) per protocol and be seen by the investigator per usual standard of care. Chemotherapies may be supplied per Section 5.1.3.2. The investigator will be expected to monitor for progression and report any SAEs and pregnancies, as outlined in Section 7.7.1.3 and Section 7.7.6. No other data will be**	To allow continued access to other study drugs for subjects who are benefiting from treatment.

	collected. The remaining subjects are considered to be on study until a discontinuation criterion is met, or the study is terminated by the sponsor.	
Section 4.1, inclusion criterion 7 and throughout document as applicable	The following revisions were made to inclusion criterion 7: b. Cohorts 1, 2, and 3: iii. If sexually active in a way that could lead to pregnancy, must consistently use ~~2 highly effective methods of birth control~~ **the acceptable combinations of contraceptive methods** (as defined in Appendix B) starting at time of informed consent and continuing throughout the study and for at least 120 days after the final dose of study drug c. Cohorts 4 and 5: iii. If sexually active in a way that could lead to pregnancy, must consistently use ~~2 highly effective methods of birth control~~ **the acceptable combinations of contraceptive methods** (as defined in Appendix B) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug	To ensure consistency with Appendix B and current Clinical Trial Facilitation and Coordination Group (CTFG) guidance
Section 4.1, inclusion criterion 8 and throughout document as applicable	The following revisions were made to inclusion criterion 8: 8. Subjects **born male** ~~who can father children~~, under the following conditions: a. Cohorts 1, 2, and 3: ii. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use **the acceptable** ~~2 highly effective~~ **combinations of contraceptive** methods ~~of birth control~~ (as defined in Appendix B) starting at time of informed consent and continuing until the final dose of study drug. iii. If sexually active with a person who is pregnant or breastfeeding, must consistently use ~~1 of 2 contraception options~~ **a condom** (as defined in Appendix B) starting at time of informed consent and continuing until the final dose of study drug b. Cohorts 4 and 5: ii. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use ~~2~~ **the acceptable** ~~highly effective~~	To ensure consistency with Appendix B and current (CTFG) guidance

	combinations of contraceptive methods ~~**of birth control**~~ (as defined in Appendix B) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug iii. If sexually active with a person who is pregnant or breastfeeding, must consistently use ~~**1 of 2 contraception options**~~ **a condom** (as defined in Appendix B) starting at time of informed consent and continuing throughout the study and for at least 6 months after the final dose of study drug	
Section 4.3	Text revised as follows: A person of childbearing potential is anyone ~~**born female**~~ who has experienced menarche and who has not undergone permanent sterilization (eg, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person over 45 years old in the absence of other biological, physiological, or pharmacological causes. A ~~**person**~~ **subject** who can ~~**father children**~~ **get someone pregnant** is anyone ~~**born male**~~ who has testes and who has not undergone permanent sterilization ~~**(eg, vasectomy followed by a clinical test proving that the procedure was effective).**~~ **(defined as bilateral orchidectomy).**	Updated to ensure consistency with Appendix B.
Section 5.1.1.2	The following revision was made to Dose and Administration. ~~**In Cycle 1**~~, **Initially**, SEA-CD40 is administered via IV infusion at a fixed infusion rate not to exceed 10 mcg/min.	Correction
Section 5.1.1.2	Added variability window for infusion rates	To provide flexibility to trial sites for minor variations in their infusion times due to mechanical variations in pumps
Section 5.1.2.1	Text revised as follows: Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in L-histidine, polysorbate **80**, sucrose, **L-methionine** and Water for Injection, United States Pharmacopeia (USP).	Correction

Section 5.1.3.2	Text revised as follows: In the US and Canada, pemetrexed and carboplatin will be sourced by study sites from commercial supply. In other countries, pemetrexed and carboplatin may ~~will~~ be provided to study sites by the sponsor **or investigational sites may use locally available marketed products authorized for use in their respective country**.	Additional information on the supply of pemetrexed and carboplatin
Section 5.2.3.2	Text revised as follows: Other allowed dose interruptions **and modifications** for pembrolizumab Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. **If a subject in Cohorts 1, 2, or 3 is unable to receive the first dose of pembrolizumab in any given cycle and is considered appropriate to receive pembrolizumab as standard of care, the subject may receive a 200 mg dose of pembrolizumab on D29 to D31 of the cycle. The subject will then continue to receive pembrolizumab at Q6W as planned on D8 of the next cycle, as long as the subject continues to be appropriate to receive pembrolizumab. If a subject requires a longer interruption of pembrolizumab for reasons other than treatment-related AEs, study intervention should** be restarted within 21 days (for Q3W dosing) or 42 days (for Q6W dosing) of the originally scheduled dose and within 42 days (for Q3W dosing) or 84 days (for Q6W dosing) of the previously administered dose, unless otherwise discussed with the sponsor. The reason for interruption is to be documented in the subject's study record.	To provide additional guidance regarding dose interruptions and Modifications for pembrolizumab
Section 5.3	Revised third bullet point under premedication and post medication to include; Ibuprofen **or other NSAIDs** (except in subjects in Cohorts 4 and 5 with CrCl <80 mL/min)	Correction
Section 5.4.3	Following revision was made to section 5.4.3 bullet point 2: Ibuprofen or other NSAIDs (including premedication) in ~~patients~~ **subjects** with CrCl <80 mL/min, during the ~~32~~**2** days	Correction

	before, the day of, and 2 days after pemetrexed administration	
Section 5.5.1.1, Table 11	The following text was added for SEA-CD40 dose modifications for Grade 2 infusion/injection or hypersensitivity reactions: **If subject has adrenal insufficiency, consider increasing replacement steroid dose to 10 mg prednisone equivalent per day on SEA-CD40 dosing days.**	To provide additional management guidance
Section 6.5	The following text was added: Subjects who discontinue treatment will continue to be assessed for response after EOT until confirmed PD or initiation of new anticancer treatment. **After SEA-CD40 drug expiry, response assessment in these patients may be continued per standard of care (SoC) at the discretion of the investigator.** Subjects who discontinue treatment due to confirmed PD or who have initiated new anticancer treatment will not be assessed for response but will be followed for survival and subsequent anticancer treatment. Follow-up may be conducted with clinic visits or telephone calls. **Survival follow-up may be discontinued at the discretion of sponsor.**	Change in IMPs
Section 6.6, SOE table and throughout document as applicable	The following text was added: All subjects will be followed for long-term survival. Assessment of survival can be done via public or hospital/medical records or a phone call. After disease progression or initiation of a new anticancer treatment, survival follow-up will be conducted, **at the discretion of the sponsor**, every 12 weeks (±1 week) for survival status until death or study closure, whichever comes first. The first survival follow-up will occur 12 weeks (±1 week) **(unless otherwise stated)** from the last radiographic scan that demonstrated disease progression or from initiation of the new anticancer treatment, as applicable. Subsequent survival follow-up will be scheduled for 12 weeks (±1 week) **(unless otherwise stated)** from the previous survival follow-up. **Timing of subsequent survival follow-up may be modified, or collection will be stopped, at the discretion of sponsor.**	Change in study design and to make these sections consistent with the Schedule of Events

Appendix B	Appendix text updated for clarity and to reflect current CTFG guidance.	Clarification and to align with current (CTFG) guidance.
Throughout document	Minor typos, formatting, and inconsistencies corrected.	Correction