Official Title: A Phase II, Randomized, Multicenter, Double-Blind, Controlled Study of Tobemstomig Plus Platinum-Based Chemotherapy Versus Pembrolizumab Plus Platinum-Based Chemotherapy in Patients with Previously Untreated Locally Advanced or Metastatic Non-Small Cell Lung Cancer

NCT Number: NCT05775289

Document Date: Protocol Amendment Version 4: 09-Nov-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, CONTROLLED STUDY OF TOBEMSTOMIG PLUS PLATINUM-BASED CHEMOTHERAPY VERSUS PEMBROLIZUMAB PLUS PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BO44178
VERSION NUMBER:	4
TEST COMPOUND:	Tobemstomig (RO7247669)
STUDY PHASE:	Phase II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 164130 EU CT Number: 2023-505211-21-00 EudraCT Number: 2022-001440-18 NCT Number: NCT05775289
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 40*58* Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocol		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on the final page of this document.	—	—	—
3	11 May 2023	—	—	—
2	31 October 2022	United States	1	19 December 2022
1	24 May 2022	—	—	—

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

[redacted]

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- [redacted]
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- [redacted]

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, CONTROLLED STUDY OF TOBEMSTOMIG PLUS PLATINUM-BASED CHEMOTHERAPY VERSUS PEMBROLIZUMAB PLUS PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED OR METASTATIC NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BO44178
VERSION NUMBER:	4
TEST COMPOUND:	Tobemstomig (RO7247669)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE II, RANDOMIZED, MULTICENTER, DOUBLE-BLIND, CONTROLLED STUDY OF TOBEMSTOMIG PLUS PLATINUM-BASED CHEMOTHERAPY VERSUS PEMBROLIZUMAB PLUS PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH PREVIOUSLY UNTREATED LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 164130 EU CT Number: 2023-505211-21-00 EudraCT Number: 2022-001440-18 NCT Number: NCT05775289

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy, safety, and pharmacokinetics of tobemstomig (also known as RO7247669) in combination with platinum-based chemotherapy compared with pembrolizumab plus platinum-based chemotherapy in participants with previously untreated, locally advanced, unresectable (Stage IIIB/IIIC) or metastatic (Stage IV) non–small cell lung cancer (NSCLC) who are not eligible to receive curative surgery and/or definitive chemoradiotherapy.

Patients with advanced or metastatic solid tumors present a great unmet need. Benefit from cancer immunotherapy with checkpoint inhibitor monoclonal antibodies, such as those targeting programmed death–1/programmed death–ligand 1 (PD-1/PD-L1), is predominantly observed in a subset of patients with inflamed tumor phenotypes. However, response is not guaranteed even in this patient subset owing to either primary or acquired resistance mechanisms. Upregulated lymphocyte activation gene 3 (LAG3) expression on T cells is associated with T-cell dysfunction, potentially resulting in adaptive resistance to anti–PD-1/PD-L1 therapies. Therefore, LAG3 blockade of tumor-infiltrating lymphocytes may overcome or prevent resistance mechanisms to anti-PD1/PD-L1 and help restore or increase T-cell proliferation and cytotoxic effector functions.

Tobemstomig concurrently targets two dominant immune checkpoint receptors, PD-1, and LAG3. Such targeting may serve to overcome resistance by means of synergic ligand blockade and subsequent re-invigoration of tumor-infiltrating lymphocytes, regardless of T-regulatory cells, and potentially delay or prevent the development of LAG3 mediated adaptive resistance mechanisms.

OBJECTIVES AND ENDPOINTS

Primary Objectives	Estimand Definitions
• To evaluate the efficacy of tobemstomig in combination with platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B)	• Population: participants with previously untreated, locally advanced, unresectable NSCLC who are ineligible for definitive chemoradiotherapy (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC of SQ or NSQ histology with no known EGFR or ALK genomic tumor aberrations • Endpoint: PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Treatment – Experimental arm NSQ NSCLC: tobemstomig in combination with pemetrexed and carboplatin, followed by maintenance tobemstomig with pemetrexed SQ NSCLC: tobemstomig in combination with paclitaxel and carboplatin, followed by tobemstomig – Control arm NSQ NSCLC: pembrolizumab in combination with pemetrexed and carboplatin, followed by maintenance pembrolizumab with pemetrexed SQ NSCLC: pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab • Intercurrent events and handling strategies: – Early discontinuation from study treatment for any reason prior to the respective event of interest: treatment policy strategy – Start of non-protocol-specified anti-cancer therapy prior to the respective event of interest: treatment policy strategy • Population-level summary: hazard ratio for PFS

ALK = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; HRQoL = health-related quality of life; PFS = progression-free survival; NSCLC = non–small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; SQ = squamous; RECIST = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Primary Objectives (cont.)	Estimand Definitions (cont.)
• To evaluate the efficacy of tobemstomig in combination with platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B)	• Population: as defined above; participants must have measurable disease at baseline, as determined by the investigator according to RECIST v1.1 • Endpoint: ORR, defined as the proportion of participants with a complete response or a partial response on two consecutive occasions 4 weeks apart, as determined by the investigator according to RECIST v1.1 • Treatment: as defined above • Intercurrent events and handling strategies: as defined above • Population-level summary: difference in ORR

ALK = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; HRQoL = health-related quality of life; PFS = progression-free survival; NSCLC = non–small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; SQ = squamous; RECIST = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of tobemstomig in combination with platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B)	• OS after randomization, defined as the time from randomization to death from any cause • Duration of response for participants with confirmed objective response, defined as the time from the first occurrence of a confirmed objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • PFS and OS in participants with PD-L1 expression, [redacted] • Change from baseline to Week 12 in patient-reported outcomes of lung cancer symptoms, physical functioning, role functioning, and global health status/quality of life, as assessed through the use of the European Organisation for Research and Treatment of Cancer Item Libraries
• To evaluate the safety of tobemstomig in combination with platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B)	• Incidence and severity of adverse events, with severity determined according to the NCI Common Terminology Criteria for Adverse Events, Version 5.0 • The severity of cytokine release syndrome will be determined according to the ASTCT Consensus Grading Scale.

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; NCI = National Cancer Institute; OS = overall survival; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; [redacted]

Secondary Objectives (cont.)	Corresponding Endpoints (cont.)
• To investigate the pharmacokinetics of tobemstomig	• PK profiles and parameters derived for tobemstomig, including, but not limited to, the following parameters, as appropriate and when data allow: – Maximum concentration – Time of maximum concentration – Clearance – Volume of distribution at steady state – Area under the concentration–time curve – Half-life • Concentrations of tobemstomig in serum at specified timepoints
• To evaluate the immune response to tobemstomig	• Prevalence of ADAs to tobemstomig at baseline and incidence of ADAs to tobemstomig during the study

ADA = anti-drug antibody; ASTCT = American Society for Transplantation and Cellular Therapy; NCI = National Cancer Institute; OS = overall survival; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; [redacted]

The primary objective for the study is expressed using the estimand framework in accordance with the International Council for Harmonisation (ICH) E9(R1) statistical principles for clinical trials (ICH 2020) (see Section 3).

In this protocol, “study treatment” refers to the combination of treatments assigned to patients as part of this study (i.e., tobemstomig or pembrolizumab in combination with pemetrexed and carboplatin or paclitaxel and carboplatin).

OVERALL DESIGN AND STUDY POPULATION

This is a randomized, Phase II, global, multicenter, double-blind study designed to evaluate the efficacy, safety, and pharmacokinetics of tobemstomig in combination with platinum-based chemotherapy compared with pembrolizumab plus platinum-based chemotherapy in patients with previously untreated, locally advanced unresectable (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC who are not eligible for curative surgery and/or definitive chemoradiotherapy.

Approximately 180 patients will be randomized in the study in a 1:1 ratio to receive either tobemstomig plus platinum-based chemotherapy (Arm A) or pembrolizumab plus platinum-based chemotherapy (Arm B).

Several key aspects of the study design and study population are summarized below.

Phase:	Phase II	**Population Type:**	Adult patients
Control Method:	Active comparator	**Population Diagnosis or Condition:**	Previously untreated, locally advanced unresectable (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC who are not eligible for curative surgery and/or definitive chemoradiotherapy.
Interventional Model:	Parallel group	**Population Age:**	18 years or over
Test Compound{s}:	Tobemstomig (also known as RO7247669)	**Site Distribution:**	Multi-site
Active Comparator:	Pembrolizumab	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 180

STUDY TREATMENT

The investigational medicinal products for this study are tobemstomig (experimental test product), pembrolizumab (comparator), carboplatin, pemetrexed, and paclitaxel.

Blinded Tobemstomig and Blinded Pembrolizumab

Participants will receive blinded tobemstomig ([redacted] mg every 3 weeks [Q3W]) or blinded pembrolizumab (200 mg Q3W) by IV infusion. Administration of study treatment will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. The [redacted]-mg dose of tobemstomig Q3W and the 200-mg dose of pembrolizumab Q3W will remain the same throughout the study.

The initial dose of tobemstomig or pembrolizumab will be delivered over [redacted] minutes by IV infusion. If the [redacted]-minute infusion is tolerated without infusion-associated adverse events (fever or chills), the second infusion may be delivered over [redacted] minutes. If the [redacted]-minute infusion is well tolerated, all subsequent infusions may be del [redacted] er [redacted] minutes.

Paclitaxel, Pemetrexed, and Carboplatin

Paclitaxel

Paclitaxel 200 mg/m^2 will be administered as an IV infusion to participants over 3 hours Q3W for four cycles as per local practice and labels. All participants should be premedicated with oral or an IV steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice. Paclitaxel should be completely administered before initiating carboplatin dose.

Pemetrexed

Pemetrexed 500 mg/m^2 will be administered to participants as an IV infusion over 10 minutes Q3W until progression or unacceptable toxicity.

All participants should receive the appropriate supplementation with vitamin B12 and folic acid and corticosteroid prophylaxis as listed below (or as per local label):

- Folic acid 350–1000 μg orally (PO): Participants must take at least five doses of folic acid 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 final dose of pemetrexed.
- Vitamin B12 1000 μg intramuscular (IM) injection: Participants will receive an IM injection the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Anti-emetic prophylaxis with dexamethasone 4 mg (or equivalent) PO twice per day: Participants should take dexamethasone the day before, the day of, and the day after pemetrexed administration. Higher or additional doses are permitted for anti-emetic prophylaxis during Cycles 1–4 are but not to exceed doses per the Multinational Association of Supportive Care and European Society of Medical Oncology.

Carboplatin

Carboplatin area under the concentration–time curve (AUC) 5 mg/mL • min: Participants will receive carboplatin as an IV infusion over 30–60 minutes Q3W for four cycles immediately after paclitaxel or pemetrexed as per local practice and labels. The dose of carboplatin should be calculated using Calvert formula (see below) and should not exceed 750 mg.

Calvert Formula:

Total dose (in milligrams [mg]) = (target AUC) × (creatine clearance [CrCl} + 25).

The estimated glomerular filtration rate used in the Calvert formula should not exceed 125 mL/min.

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

Paclitaxel, pemetrexed, and carboplatin will be administered to participants as outlined in the following table.

Treatment Regimen for Pemetrexed, Paclitaxel, and Carboplatin

Study Treatment	Dose and Route of Administration	Induction Period (Four 21-Day Cycles)	Maintenance (until PD)
Pemetrexed	500 mg/m^2 by IV infusion	Over approximately 10 minutes on Day 1 Q3W	Over approximately 10 minutes on Day 1 Q3W
Paclitaxel	200 mg/m^2 by IV infusion	Over approximately 3 hours on Day 1 Q3W	Not applicable
Carboplatin	AUC 5 mg/mL • min by IV infusion	Over approximately 30–60 minutes on Day 1 Q3W	Not applicable

AUC = area under the concentration–time curve; PD = progressive disease; Q3W = every 3 weeks.

Dose modifications of tobemstomig, including dose reductions, will not be allowed in this study.

DURATION OF PARTICIPATION

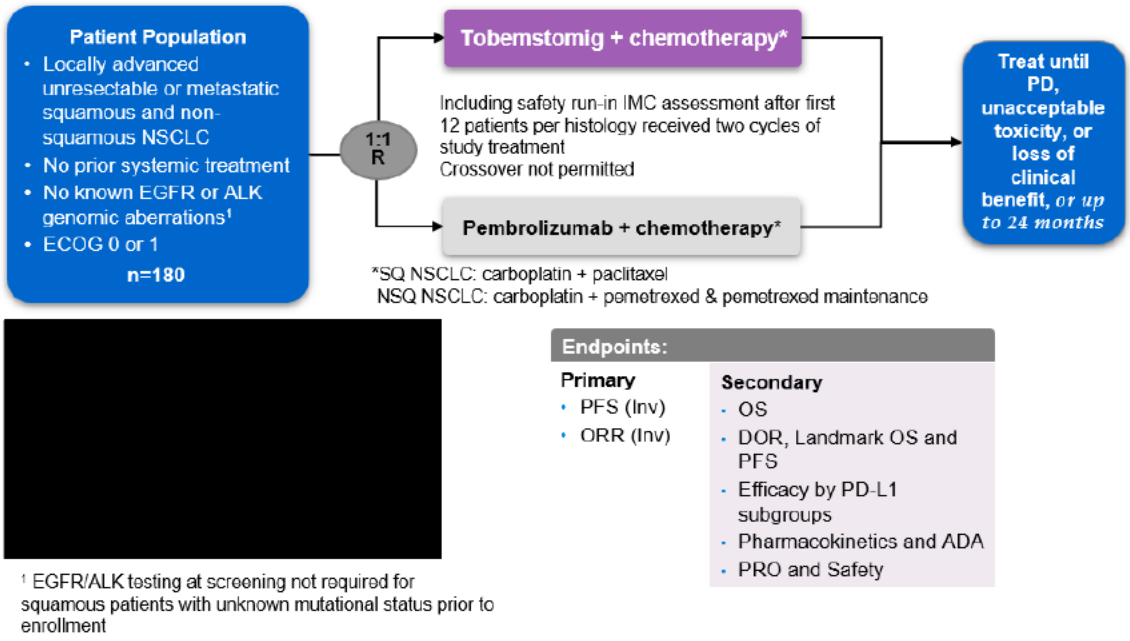
Treatment will continue until disease progression per Response Evaluation Criteria in Solid Tumors version 1.1, unacceptable toxicity, *or* loss of clinical benefit as determined by the investigator (see Section 7.1 for additional details), *up to 24 months,* or until the Sponsor decides to terminate the study, whichever comes first. The total duration of study participation for each individual is expected to range from 1 day to approximately *28* months. Participants will be allowed to continue treatment beyond disease progression *for up to 24 months if prespecified* criteria are met (Section 4.2.5).

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	*Not applicable*

1.2 STUDY SCHEMA

Figure 1 Study Schema



ADA = anti-drug antibody; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IMC = Internal Monitoring Committee; Inv = investigator; NSCLC = non–small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; PRO = patient-reported outcome; R = randomization; SQ = squamous; [redacted]

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULE

Table 1 Schedule of Activities

Procedure or Assessment	Screening [a]	Treatment Cycle (21-Day Cycles or Q3W) [b]						Treatment Discontinuation Visit [c]	*Safety* Follow-Up *Visit* [d]
		Induction (Cycles 1–4) [e]			Maintenance (Cycles 5+)			≤ 30 Days after Final Dose of Study Treatment	*90 Days after Final Dose of Study Treatment*
	Days −28 to −1	Day 1 (±3 Days)	Day 8 *(±3 days)*	Day 15 *(±3 days)*	Day 1 (±3 days)	Day 8 *(±3 days)*	Day 15 *(±3 days)*		
Informed Consent Forms: [f] Main ICF for study participation Research Biosample Repository (RBR) *ICF*	x								
Demographics	x								
Medical and cancer history and baseline conditions [g]	x								
Vital signs [h]	x	x			x			x	
Weight	x	x			x			x	
Height	x								
Complete physical examination [i]	x								
Limited physical examination [j]		x			x			x	
ECOG Performance Status [k]	x	x			x			x	
12-Lead ECG [l]	x	Perform Cycle 1 & 5 and as clinically indicated. [l]						x	
TTE or MUGA [m]	x								
Hematology [n, o]	x	x			x			x	
Serum chemistry panel [p, o]	x	x			x			x	

Table 1 Schedule of Activities (cont.)

Procedure or Assessment	Screening [a]	Treatment Cycle (21-Day Cycles or Q3W) [b]						Treatment Discontinuation Visit [c]	*Safety* Follow-Up *Visit* [d]
		Induction (Cycles 1–4) [e]			Maintenance (Cycles 5+)				
	Days −28 to −1	Day 1 (±3 Days)	Day 8 *(±3 days)*	Day 15 *(±3 days)*	Day 1 (±3 days)	Day 8 *(±3 days)*	Day 15 *(±3 days)*	≤30 Days after Final Dose of Study Treatment	*90 Days after Final Dose of Study Treatment*
Coagulation: INR and aPTT [o]	x							x	
Cardiac enzymes: troponin T or troponin I	x	x			x				
Thyroid function: TSH, free T3, and free T4 [q]	x	x [q]			x [q]			x	
HIV, HBV, HCV serology [r]	x								
Urinalysis [s]	x	Perform as clinically indicated.							
Pregnancy test (for women of childbearing potential only) [t]	x	x			x			x	
CT scan with contrast of brain (or MRI scan)	x [u]								
Induction treatment administration [e] Arm A, participants with NSQ NSCLC: tobemstomig+ pemetrexed + carboplatin		x							
Arm A, participants with SQ NSCLC: tobemstomig+ paclitaxel + carboplatin		x							

Table 1 Schedule of Activities (cont.)

Procedure or Assessment	Screening [a]	Treatment Cycle (21-Day Cycles or Q3W) [b]						Treatment Discontinuation Visit [c]	*Safety* Follow-Up *Visit* [d]
		Induction (Cycles 1–4) [e]			Maintenance (Cycles 5+)				
	Days −28 to −1	Day 1 (±3 Days)	Day 8 *(±3 days)*	Day 15 *(±3 days)*	Day 1 (±3 days)	Day 8 *(±3 days)*	Day 15 *(±3 days)*	≤30 Days after Final Dose of Study Treatment	*90 Days after Final Dose of Study Treatment*
Arm B, participants with NSQ NSCLC: pembrolizumab + pemetrexed + carboplatin		x							
Arm B, participants with SQ NSCLC: pembrolizumab + paclitaxel + carboplatin		x							
Maintenance treatment administration									
Arm A, participants with NSQ NSCLC: tobemstomig + pemetrexed					x				
Arm A, participants with SQ NSCLC: tobemstomig					x				
Arm B, participants with NSQ NSCLC: pembrolizumab + pemetrexed					x				
Arm B, participants with SQ NSCLC: pembrolizumab					x				
Tumor response [u, v]	x	Every *12* weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 and every *12* weeks (±7 days) thereafter, regardless of treatment delays							

Table 1 Schedule of Activities (cont.)

Procedure or Assessment	Screening [a]	Treatment Cycle (21-Day Cycles or Q3W) [b]						Treatment Discontinuation Visit [c]	*Safety* Follow-Up *Visit* [d]
		Induction (Cycles 1–4) [e]			Maintenance (Cycles 5+)				
	Days −28 to −1	Day 1 (±3 Days)	Day 8 *(±3 days)*	Day 15 *(±3 days)*	Day 1 (±3 days)	Day 8 *(±3 days)*	Day 15 *(±3 days)*	≤30 Days after Final Dose of Study Treatment	*90 Days after Final Dose of Study Treatment*
[redacted]	[redacted]								
Adverse events [w]		x			x			x	x
Concomitant medications [x]	x	x			x			x	

[redacted] CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EOI = end of infusion; FFPE = formalin-fixed, paraffin-embedded; ICF = Informed Consent Form; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HbsAb = hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = Informed Consent Form; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; PD = pharmacodynamic; [redacted] Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TTE = transthoracic echocardiogram.

Notes: All assessments should be performed within ±3 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Screening tests and evaluations will be performed within 28 days prior to Day 1 of Cycle 1, unless otherwise specified. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening. Screening assessments performed ≤96 hours prior to Day 1 of Cycle 1 are not required to be repeated on Day 1 of Cycle 1.

[b] During the treatment period, assessments scheduled on the day of study treatment infusions should be performed prior to infusion unless otherwise specified. [redacted], *treatment beyond 24 months is no longer permitted in either treatment arm. Patients who are continuing treatment beyond 24 months must discontinue from the study and seek other treatment options outside of the study.*

[c] Participants will be asked to return to the clinic for a treatment discontinuation visit no more than 30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[d] After study treatment has been discontinued, *safety* information will be collected by telephone and/or clinic visits *for 90 days after the last dose of study treatment has been received.*

Table 1 Schedule of Activities (cont.)

[e] During the induction phase, the number of chemotherapy cycles counts toward the prespecified number of induction cycles (four), provided that at least one chemotherapy component has been administered. Cycles when no chemotherapy is given do not count toward the total number of induction chemotherapy cycles.

[f] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[g] Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of drugs of abuse, and baseline medical conditions will be recorded at baseline.

[h] Vital signs include respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature (see Table 6 for details regarding recording of vital signs during administration of study treatment). New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

[i] A complete physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[j] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. New or worsened clinically significant abnormalities should be recorded as adverse events in the Adverse Event eCRF. Limited physical examinations may be performed ≤96 hours before Day 1 of each cycle.

[k] Status will be measured with use of the ECOG Performance Status Scale and may be performed ≤96 hours before Day 1 of each cycle.

[l] Single 12-lead ECG is required at screening, at the treatment discontinuation visit, Cycle 1 and Cycle 5 predose *and end of study treatment infusion (30 [±10] minutes after completion)* and when clinically indicated. Electrocardiograms for each participant should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. Electrocardiogram recordings must be performed after the participant has been resting in a supine position for at least 10 minutes.

[m] TTE or MUGA scan will be performed at screening if no scan is available within 6 months prior to randomization. Scans may be repeated at the investigator's discretion if there are signs or symptoms of cardiotoxicity.

[n] Hematology includes WBC count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes), RBC count, hemoglobin, hematocrit, platelet count, and differential count. Assessment may be performed ≤96 hours before Day 1 of each cycle.

[o] Screening laboratory tests must be performed within 14 days prior to initiation of study treatment. For details, refer to Section 5.1 (Inclusion Criteria).

[p] Chemistry panel (serum) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, magnesium, potassium, chloride, calcium, phosphate, glucose, BUN or urea, creatinine, total protein, albumin, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase. Assessment may be performed ≤96 hours prior to Day 1 of each cycle.

[q] Thyroid-stimulating hormone and free T3 (or total T3 at sites where T3 is not performed), and free T4 will be assessed at screening, on Day 1 of Cycle 1, every fourth cycle thereafter (e.g., Cycles 5, 9, 13, and so forth), and at treatment discontinuation. Assessment may be performed ≤96 hours prior to Day 1 of each cycle when it is required.

[r] At screening, all patients will be tested for HIV, HbsAg, HbsAb, total HBcAb, and HCV antibodies. If a patient has negative HBsAg and HBsAb tests and a positive total HBcAb test at screening, an HBV DNA test must also be performed. If a patient has a positive HCV antibody test at

Table 1 Schedule of Activities (cont.)

screening, an HCV RNA test must also be performed. Individuals with a positive HIV test at screening are eligible, provided they are stable on anti-retroviral therapy, have a CD4 count ≥200/mL, and have an undetectable viral load.

[s] Urinalysis by dipstick (specific gravity, pH, glucose, protein, ketones, and blood). Urinalysis is required at screening and will be obtained when clinically indicated. Assessment may be performed ≤96 hours before Day 1 of each cycle.

[t] All women of childbearing potential will have a serum pregnancy test during screening within 14 days prior to initiation of study drug. Urine pregnancy tests will be performed ≤ 96 hours prior to Day 1 of every cycle and at the study treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. An at-home pregnancy test will be provided. The test has to be conducted 4 months after the final dose (for women of childbearing potential), and the site will inquire about the result during the second follow-up visit.

[u] All known sites of disease, including measurable and/or non-measurable disease, must be documented at screening and re-assessed at each subsequent tumor evaluation. Screening and subsequent tumor assessments must include CT scans (with oral or IV contrast unless contraindicated). A CT scan of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. MRI scans with contrast of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest may be used for participants for whom CT scans with contrast are contraindicated (i.e., participants with contrast allergy or impaired renal clearance). A CT (with contrast if not contraindicated) or MRI scan of the head must be performed at screening to evaluate CNS metastasis in all participants. MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. At subsequent (postscreening) tumor assessments, participants with a history of irradiated brain metastases at screening are not required to undergo brain scans unless clinically indicated (e.g., in participants with neurologic symptoms). If a CT scan for tumor assessment is performed in a positron emission tomography/CT scanner, CT acquisition must be consistent with the standards for a full contrast diagnostic CT scan. Further investigations, such as bone scans and CT scans of the neck, should also be performed if clinically indicated.

[v] Participants will undergo tumor assessments at baseline and every *12* weeks (±7 days) for 48 weeks following Day 1 of Cycle 1 regardless of treatment delays. After the completion of the Week 48 tumor assessment, tumor assessments are required every *12* weeks (±7 days) regardless of treatment delays until radiographic disease progression per RECIST v1.1 (see Appendix 10), withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first. Participants who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments every *12* weeks (±2 weeks) after initial documentation of progression or more frequently, if clinically indicated, regardless of time in study, until treatment is discontinued.

At the investigator's discretion, scans may be performed at any time if progressive disease or loss of clinical benefit is suspected. The investigator's assessment of overall tumor response at all timepoints should be based on RECIST v1.1 only. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle. Participants who discontinue treatment for reasons other than radiographic disease progression (e.g., toxicity, symptomatic deterioration) will continue the same schedule of tumor assessments as described above until radiographic disease progression, withdrawal of consent, death, or study termination by Sponsor, whichever occurs first. In the absence of radiographic disease progression, tumor assessments should continue regardless of whether a participant starts a new anti-cancer therapy.

Table 1 Schedule of Activities (cont.)

[w] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. All serious adverse events will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. In addition, adverse events of special interest (refer to Section A3–5) will continue to be reported until 90 days after the final dose of study treatment, regardless of initiation of new systemic anti-cancer therapy. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment. Every effort should be made to follow all serious adverse events considered to be related to study treatment or protocol-related procedures until a final outcome can be reported.

[x] Medication (e.g., prescription drugs, over-the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) and vaccines used by a patient in addition to protocol-mandated treatment used within 7 days prior to the initiation of study treatment should be documented. At subsequent visits, changes to current medications or medications used since the last documentation will be recorded.

[redacted]

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to evaluate the efficacy, safety, and pharmacokinetics of tobemstomig (also known as RO7247669) in combination with platinum-based chemotherapy compared with pembrolizumab plus platinum-based chemotherapy in participants with previously untreated, locally advanced, unresectable (Stage IIIB/IIIC) or metastatic (Stage IV) non–small cell lung cancer (NSCLC) who are not eligible to receive curative surgery and/or definitive chemoradiotherapy.

2.2 BACKGROUND

Lung cancer remains the leading cause of cancer deaths worldwide. NSCLC accounts for approximately 85% of all cases of lung cancer (Molina et al. 2008; Howlader et al. 2018). NSCLC can be divided into two subcategories: squamous (SQ) and non-squamous (NSQ). SQ cell histology accounts for approximately 25% of NSCLCs (Langer et al. 2010). NSQ NSCLC includes several histologic subtypes, the most common of which is adenocarcinoma, which accounts for more than half of all NSCLC cases. The remaining cases of NSCLC are represented by other NSQ NSCLC histologies, including large cell carcinoma, neuroendocrine tumors, sarcomatoid carcinoma, and those with poorly differentiated histology.

Standard of care treatment for patients with advanced NSQ NSCLC in the first-line setting is largely driven by results of molecular profiling. The preferred first-line treatment for patients with tumors harboring an oncogenic driver mutation utilizes an approved targeted therapy, if available. For patients whose tumors lack a targetable oncogenic aberration, current standard of care treatment regimens in the first-line setting typically consist of an immune checkpoint inhibitor (CPI), including programmed death–1 (PD-1)– and programmed death-ligand 1 (PD-L1)–blocking antibodies, with or without platinum-based doublet chemotherapy and bevacizumab. The current standard of care for newly diagnosed patients with advanced-stage SQ NSCLC includes paclitaxel or gemcitabine in combination with a platinum agent.

Despite significant advances with combination immunotherapy and the approval of immune CPI agents in combination with chemotherapy as first-line therapy for patients with advanced NSCLC, the majority of patients with advanced NSCLC progress during treatment and ultimately experience disease progression and succumb to this disease. Therefore, a high unmet medical need persists for patients with advanced NSCLC. To improve treatment outcomes for patients with NSCLC, multiple combinations with anti–PD-L1 therapies are being assessed.

Tobemstomig is a novel, fragment crystallizable (Fc)-silent IgG1-based bispecific antibody (BsAb) in a 1+1 format that incorporates monovalent binding to the checkpoint receptors, PD-1 and lymphocyte activation gene 3 (LAG3). Use of a natural IgG-like monovalent heterodimeric IgG1 format allows the antibody to concurrently bind to PD-1

and LAG3. The tobemstomig BsAb is engineered to preferentially bind to T cells that co-express both PD-1 and LAG3 and to a lesser extent, either PD-1 or LAG3 alone. Monovalent binding to LAG3 reduces internalization of the antibody upon binding to the T-cell surface, and the retention time of tobemstomig on T-cell surface is higher when bound to PD-1 and LAG3. PGLALA mutations have been introduced into the IgG1-based Fc region of tobemstomig. This avoids drug-shaving and thus development of tumor-associated macrophage resistance mechanisms that have been observed with IgG4-based antibodies such as Keytruda® (pembrolizumab) and Opdivo® (nivolumab) (Arlauckas et al. 2017).

A detailed description of the chemistry, pharmacology, and safety of tobemstomig is provided in the Tobemstomig Investigator's Brochure.

2.2.1 The PD-L1/PD-1 Pathway

Encouraging clinical data in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

The PD-1/PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-1 is an inhibitory receptor that is expressed on activated and exhausted T cells, including tumor-infiltrating $CD8^+$ T cells that recognize mutated tumor antigens (neo-antigens). Binding of PD-L1 to PD-1 inhibits T-cell proliferation, activation, cytokine production, and cytolytic activity, leading to a functionally inactivated and exhausted T-cell state (Butte et al. 2007; Yang et al. 2011). Therapeutic targeting of the PD-1/PD-L1 pathway to enhance anti-tumor T-cell responses has been clinically validated across multiple solid tumors when given both as a single-agent treatment and in combination with chemotherapy and other targeted agents.

2.2.2 The LAG3 Pathway

LAG3 is an immune checkpoint protein involved in the regulation of anti-tumor immunity and chronic infection. LAG3 is expressed on activated T cells, B cells, natural killer cells, and a subset of tolerogenic plasmacytoid dendritic cells, and constitutively on T-regulatory cells (Huard et al. 1994). Structurally similar to CD4, LAG3 is a member of the Ig superfamily and binds to major histocompatibility complex class II (MHC-II). The interaction of LAG3 with MHC-II inhibits T-cell proliferation, activation, cytolytic function, and proinflammatory cytokine production (Goldberg and Drake 2011). The effect of LAG3 expression on T-regulatory cells is controversial. An early report concluded that LAG3 expression promotes T-regulatory cell–mediated immune suppression (Camisaschi et al. 2010). However, a more recent report describes LAG3 limiting T regulatory cell–mediated immune suppression (Zhang et al. 2017).

Expression of LAG3 has been reported across various tumor types, including NSCLC, hepatocellular carcinoma, breast cancer, ovarian cancer, melanoma, renal cell carcinoma, and prostate cancer, and is associated with poor prognosis (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015; He et al. 2016; Norström et al. 2016). Clinical evaluation of anti-LAG3 agents, given as a single agent and in combination with other CPIs, is ongoing in several early-phase studies in patients with advance solid tumors (Long et al. 2018). Preliminary data demonstrate that anti-LAG3 therapy is well tolerated as a single agent and in combination with anti–PD-1 therapies, and the safety profiles were consistent with those of other CPI treatments (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018).

Taken together, therapeutic targeting of LAG3 may represent an attractive strategy for the treatment of patients with NSCLC.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the efficacy, safety, and pharmacokinetics of tobemstomig, a novel immunomodulating therapy, in combination with platinum-based chemotherapy to address a significant unmet medical need in patients with previously untreated, locally advanced unresectable (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC who are not eligible for curative surgery and/or definitive chemoradiotherapy.

Patients with advanced or metastatic solid tumors present a great unmet need. Benefit from cancer immunotherapy with CPI monoclonal antibodies, such as those targeting PD-1/ PD-L1, is predominantly observed in a subset of patients with inflamed tumor phenotypes. However, response is not guaranteed even in this patient subset owing to either primary or acquired resistance mechanisms. Upregulated LAG3 expression on T cells is associated with T-cell dysfunction, potentially resulting in adaptive resistance to anti–PD-1/PD-L1 therapies (Sharma et al. 2017). Therefore, LAG3 blockade of tumor-infiltrating lymphocytes (TILs) may overcome or prevent resistance mechanisms to anti–PD-1/PD-L1 and help restore or increase T-cell proliferation and cytotoxic effector functions.

Tobemstomig concurrently targets two dominant immune-checkpoint receptors, PD-1 and LAG3. Such targeting may serve to overcome resistance by means of synergic ligand blockade and subsequent re-invigoration of TILs, regardless of T-regulatory cells, and potentially delay or prevent the development of LAG3-mediated adaptive resistance mechanisms.

Up to the clinical cut-off date of 1 March 2022, tobemstomig has been tolerated at doses of up to 2100 mg every 2 weeks (Q2W); AEs have been manageable, and the safety profile is observed to be consistent across different solid tumor indications including NSCLC as well as with approved PD-1 directed antibodies.

Relevant efficacy and safety data up to the data cut-off date of 1 March 2022 for tobemstomig are currently available from Study NP41300, a Phase I study in patients with advanced and/or metastatic solid tumors.

In the dose escalation part of the study NP41300 the disease control rate (DCR) was 51.4% (18 of 35 evaluable participants) and the objective response rate (ORR) was 17.1% (6 of 35 participants). [redacted]

[redacted]

[redacted]

Preliminary clinical results suggest that combination treatment with anti–PD-1 (nivolumab) and anti-LAG3 (relatlimab) agents has the potential for increased benefit compared with anti–PD-1 therapy alone, while having an acceptable safety profile similar to the safety profile of nivolumab monotherapy. In patients with advanced melanoma previously treated with anti–PD-1/PD-L1 therapy, the objective response rate (ORR) of the combination was 11.5% (n = 61), with a disease control rate of 49% (Ascierto et al. 2017).

Tawbi et al. (2022) reported results from the completed Phase III trial, RELATIVITY-047 (CA224-047; NCT03470922), assessing the efficacy and safety of dual inhibition of LAG3 and PD-1 therapies in combination with relatlimab, a human IgG4 LAG3-blocking antibody, and nivolumab, a PD-1–blocking antibody, compared with standard-care nivolumab alone. The study enrolled 714 previously untreated patients with

histologically confirmed, unresectable Stage III or IV melanoma. Patients were stratified according to LAG3 expression, PD-L1 expression, *BRAF* mutation status, and metastatic stage. The primary efficacy endpoint was PFS, as determined by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Secondary endpoints included overall survival (OS) and ORR (Tawbi et al. 2022).

Blinded independent assessment of PFS was longer with relatlimab plus nivolumab than with nivolumab. Patients treated with relatlimab plus nivolumab had twice the median PFS and a 25% lower risk of disease progression or death than nivolumab alone (hazard ratio [HR]: 0.75; $p = 0.006$ by the log-rank test). A 12% difference in landmark PFS between the groups was observed at 12 months. The longer PFS with relatlimab plus nivolumab than with single-agent nivolumab was associated with a slightly greater incidence of adverse events and a health-related quality of life (HRQoL) measures similar to that observed with nivolumab. Combination treatment with relatlimab and nivolumab also showed a PFS benefit over nivolumab in prespecified subgroups. Patients with characteristics that are typically associated with a worse prognosis, such as visceral metastases, high tumor burden, elevated levels of serum lactate dehydrogenase, or mucosal or acral melanoma, had improved outcomes. Expression of LAG3 or PD-L1 was not predictive of PFS benefit with combination treatment with relatlimab plus nivolumab over nivolumab. However, a benefit of combination treatment with relatlimab and nivolumab over nivolumab was observed across *BRAF*-mutant and wild-type subgroups (Tawbi et al. 2022).

Confirmed ORR by BICR was numerically increased from 32.6% (95% CI: 27.8 to 37.7) with nivolumab alone to 43.1% (95% CI: 37.9 to 48.4) in the relatlimab plus nivolumab treatment group. Moreover, a non-statistically significant improvement in OS was also observed with relatlimab plus nivolumab over nivolumab alone corresponding to an HR of 0.80 (95% CI: 27.8 to 37.7). Median OS was not reached (95% CI: 34.2 to not reached) compared with 34.1 months (95% CI: 25.2 to not reached), respectively.

A total of 470 patients (65.8%) discontinued treatment (237 patients [66.8%] in the relatlimab plus nivolumab group and 233 patients [64.9%] in the nivolumab group), with most discontinuations attributed to disease progression (reported in 36.3% and 46.0% of patients, respectively) (Tawbi et al. 2022).

Infusion-related adverse reactions occurred in 5.9% of patients who received combination treatment with relatlimab and nivolumab compared with 3.6% of patients who received nivolumab. Grade 3 or 4 treatment-related adverse events occurred in 18.9% of patients in the relatlimab plus nivolumab group and in 9.7% in the nivolumab group. The most common Grade 3 or 4 treatment-related adverse events in the relatlimab plus nivolumab group included increased levels of lipase (in 1.7% of the patients), ALT (1.4%), and AST (1.4%), as well as fatigue (1.1%). Treatment-related adverse events (of any grade) leading to discontinuation were experienced by 14.6% of

patients in the relatlimab plus nivolumab group compared with 6.7% of those in the nivolumab group. In all, five treatment-related deaths were reported and considered by investigators to be related to treatment: three deaths in patients in the relatlimab plus nivolumab group (0.8%) (hemophagocytic lymphohistiocytosis, acute pulmonary edema, and pneumonitis) and two deaths in the nivolumab group (0.6%) (sepsis and myocarditis in 1 patient and pneumonia in 1 patient). The most common categories of immune-related adverse events reported in the relatlimab plus nivolumab group were hypothyroidism or thyroiditis (in 18.0% of the patients), rash (9.3%), and diarrhea or colitis (6.8%) (Tawbi et al. 2022).

Given that the mechanisms for optimal targeting of immune regulation in the tumor environment are still under exploration, rational new approaches to increase response rates to first-line CPI therapy are warranted. Untreated patients with advanced and metastatic NSCLC may benefit from first-line treatment with a PD-1/LAG3 BsAb if in fact the additional targeting of LAG3 conveys additive anti-tumor activity beyond that expected with PD-1 targeting alone.

Treatment-related adverse events with anti–PD-1 CPI monotherapy include events associated with autoimmune activation, such as thyroiditis, hepatitis, colitis, nephrotoxicity, adrenal insufficiency, pneumonitis, and less commonly, neurotoxicity, and myocarditis. The costimulatory action of tobemstomig on PD-1 and LAG3 receptors, might bear the risk of exaggerated immune cell (IC) activation, particularly given LAG3 modulation. The preliminary data from recent early-phase studies of anti-LAG3 antibodies showed generally anti-LAG3 therapy was well tolerated given as a monotherapy and in combination with anti–PD-1 therapies and that the safety profile was consistent with that of the other CPI agents (Ascierto et al. 2017; Hong et al. 2018; Stratton et al. 2018).

Precautions against general risks for patients have been taken into account in the safety measures in this study, which include stringent inclusion and exclusion criteria (Section 5) and rules for treatment interruption and withdrawal from the study (Section 7). The re-invigorating action of tobemstomig on immune effector cells may result in the occurrence of enhanced, untoward, immune-mediated adverse events and increase in cytokine release–mediated toxicities. Recommendations for prophylaxis and management of specific and known PD-1/PD-L1–mediated adverse events are presented in Appendix 6.

Administration of therapeutic antibodies may cause infusion-related reactions (IRRs) and the formation of anti-drug antibodies (ADAs). *IRR is an identified* risk *associated with* tobemstomig *that has been reported across the tobemstomig clinical development program, most commonly at mild-to-moderate severity or intensity. Additionally,*

[redacted]

[redacted]

In a non–Good Laboratory Practice (GLP), dose range–finding, pharmacokinetic (PK) and progressive disease study and a 4-week GLP study in cynomolgus monkeys, ADA development was observed independent of dose. No adverse findings were observed, and no toxicity related to ADA formation was observed. *To date, no ADA impact on exposure has been detected at the population level.* Any clinical signs and symptoms suggestive of a hypersensitivity reaction, in particular an immune complex–mediated reaction, will be carefully investigated. *Participants with these signs and symptoms will be monitored for development of ADA formation.*

Refer to Appendix 6 for information on the anticipated risks for tobemstomig and risk-mitigation measures, including guidelines for managing adverse events associated with tobemstomig.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of tobemstomig are presented in the Tobemstomig Investigator's Brochure.

Based on the considerations above, and the planned safety monitoring and management guidance, the proposed study treatments are considered to have an appropriate benefit–risk profile for the population included in this study.

COVID-19 Benefit–Risk Assessment

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities (including those with cancer) are a more vulnerable population. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses. It is unclear how immunotherapy affects the incidence or severity of COVID-19. It is not anticipated that treatment with tobemstomig will increase the risk of infection with SARS-CoV-2. Severe COVID-19 is associated with cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin-6, interleukin-10, interleukin-2, and interferon-γ. Tobemstomig has a low-risk of CRS and, while it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a participant develops SARS-CoV-2 infection while receiving tobemstomig. At this time, there is insufficient evidence for causal association between tobemstomig and an increased risk of severe outcomes from COVID-19.

There are limited data concerning the possible interactions between cancer immunotherapy and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively affect the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).

Per recommendations of the National Cancer Comprehensive Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune CPIs), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving tobemstomig, a decision to administer the vaccine to a participant should be made by the investigator on an individual basis in consultation with the participant.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving tobemstomig to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefits from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. In this study, receipt of a COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 6.8.1).

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

This Phase II study will evaluate the efficacy, safety, and pharmacokinetics of tobemstomig in combination with platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B) in participants with previously untreated, locally advanced, unresectable (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC who are not eligible to receive curative surgery and/or definitive chemoradiotherapy.

In this protocol, “study treatment” refers to the combination of treatments assigned to patients as part of this study (i.e., tobemstomig or pembrolizumab in combination with pemetrexed and carboplatin or paclitaxel and carboplatin).

Table 3 presents the primary objectives for the study expressed using the estimand framework in accordance with the International Council for Harmonisation (ICH) E9(R1) statistical principles for clinical trials (ICH 2020). Table 4 presents the secondary and exploratory objectives and corresponding endpoints.

Table 3 Primary Objectives and Corresponding Estimands

Primary Objectives	Estimand Definitions
• To evaluate the efficacy of tobemstomig in combination with platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B)	• Population: participants with previously untreated, locally advanced, unresectable NSCLC who are ineligible for definitive chemoradiotherapy (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC of SQ or NSQ histology with no known EGFR or ALK genomic tumor aberrations (Refer to Section 5.2) • Endpoint: PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • Treatment – Experimental arm NSQ NSCLC: tobemstomig in combination with pemetrexed and carboplatin, followed by maintenance tobemstomig with pemetrexed SQ NSCLC: tobemstomig in combination with paclitaxel and carboplatin, followed by tobemstomig – Control arm NSQ NSCLC: pembrolizumab in combination with pemetrexed and carboplatin, followed by maintenance pembrolizumab with pemetrexed SQ NSCLC: pembrolizumab in combination with paclitaxel and carboplatin, followed by pembrolizumab • Intercurrent events and handling strategies: – Early discontinuation from study treatment for any reason prior to the respective event of interest: treatment policy strategy – Start of non–protocol-specified anti-cancer therapy prior to the respective event of interest: treatment policy strategy • Population-level summary: hazard ratio for PFS

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; PFS = progression-free survival; NSCLC = non–small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; SQ = squamous; RECIST = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Table 3 Primary Objectives and Corresponding Estimands (cont.)

Primary Objectives	Estimand Definitions
• To evaluate the efficacy of tobemstomig in combination with platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B)	• Population: as defined above; participants must have measurable disease at baseline, as determined by the investigator according to RECIST v1.1 • Endpoint: ORR, defined as the proportion of participants with a complete response or a partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 • Treatment: as defined above • Intercurrent events and handling strategies: as defined above • Population-level summary: difference in ORR

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; HRQoL = health-related quality of life; PFS = progression-free survival; NSCLC = non–small cell lung cancer; NSQ = non-squamous; ORR = objective response rate; OS = overall survival; SQ = squamous; RECIST = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Table 4 Secondary and Exploratory Objectives and Endpoints

Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of tobemstomig in combination with platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B)	• OS after randomization, defined as the time from randomization to death from any cause • Duration of response for participants with confirmed objective response, defined as the time from the first occurrence of a confirmed objective response to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • PFS and OS in participants with PD-L1 expression, [redacted] • Change from baseline to Week 12 in patient-reported outcomes of lung cancer symptoms, physical functioning, role functioning, and global health status/quality of life, as assessed through the use of the European Organisation for Research and Treatment of Cancer Item Libraries
• To evaluate the safety of tobemstomig plus platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B)	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE, Version 5.0 • The severity of cytokine release syndrome will be determined according to the ASTCT Consensus Grading Scale.
• To investigate the pharmacokinetics of tobemstomig	• PK profiles and parameters derived for tobemstomig, including, but not limited to, the following parameters, as appropriate and when data allow: – Maximum concentration – Time of maximum concentration – Clearance – Volume of distribution at steady state – Area under the concentration–time curve – Half-life • Concentrations of tobemstomig in serum at specified timepoints
• To evaluate the immune response to tobemstomig	• Prevalence of ADAs to tobemstomig at baseline and incidence of ADAs to tobemstomig during the study

ADA = anti-drug antibody; ASTCT = American Society of Transplantation and Cellular Therapy; NCI = National Cancer Institute; OS = overall survival; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; [redacted]

Table 4 Secondary and Exploratory Objectives and Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• To evaluate the tolerability of tobemstomig plus platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B) from the participant's perspective	• Presence, frequency of occurrence, severity, and/or degree of interference with daily function of symptomatic treatment toxicities (specify as relevant for treatments included in study (i.e., tobemstomig, pembrolizumab, chemotherapy), as assessed through use of the NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events • Frequency of participants' response of the degree to which they are troubled with treatment symptoms, as assessed through use of the EORTC Item Library 46
• To evaluate potential effects of ADAs	• Relationship between tobemstomig ADA status and efficacy, safety, or PK endpoints
• To assess the predictive and prognostic effect(s) of exploratory biomarkers in tissue and blood, and their association with disease status, mechanisms of resistance, and/or response to study drug • In addition biomarkers will also be assessed for association with susceptibility to developing adverse events (i.e., safety biomarkers), evidence of tobemstomig activity (i.e., pharmacodynamic biomarkers), or may increase the knowledge and understanding of disease biology and drug safety or pharmacokinetics	• Relationship between biomarkers in blood and tumor tissue and efficacy, safety, PK, or other biomarker endpoints

ADA = anti-drug antibody; ASTCT = American Society of Transplantation and Cellular Therapy; NCI = National Cancer Institute; OS = overall survival; PD-L1 = programmed death–ligand 1; PFS = progression-free survival; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; [redacted]

4. STUDY DESIGN

[redacted]

[redacted]

4.2 OVERALL DESIGN

This is a randomized, Phase II, global, multicenter, double-blind study designed to evaluate the efficacy, safety, and pharmacokinetics of tobemstomig in combination with platinum-based chemotherapy compared with pembrolizumab plus platinum-based chemotherapy in patients with previously untreated, locally advanced unresectable (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC who are not eligible for curative surgery and/or definitive chemoradiotherapy.

Approximately 180 patients will be randomized in the study in a 1:1 ratio to receive either tobemstomig plus platinum-based chemotherapy (Arm A) or pembrolizumab plus platinum-based chemotherapy (Arm B) as follows:

- **Arm A (n=~90): Tobemstomig plus platinum-based chemotherapy**
  - Participants with NSQ NSCLC will receive induction treatment with blinded tobemstomig in combination with pemetrexed and carboplatin, all on Day 1 every 3 weeks (Q3W) for four 21-day cycles, followed by Q3W maintenance therapy with blinded tobemstomig together with pemetrexed until disease progression or treatment discontinuation *for a maximum of 24 months of treatment*.
  - Participants with SQ NSCLC will receive blinded tobemstomig in combination with paclitaxel and carboplatin, all on Day 1 Q3W for four 21-day cycles, followed by blinded tobemstomig (on Day 1) Q3W until disease progression or treatment discontinuation *for a maximum of 24 months of treatment*.
- **Arm B (n=~90): Pembrolizumab plus platinum-based chemotherapy**
  - Participants with NSQ NSCLC will receive induction treatment with blinded pembrolizumab in combination with pemetrexed and carboplatin, all on Day 1 Q3W for four 21-day cycles, followed by a maintenance therapy with blinded pembrolizumab together with pemetrexed Q3W until disease progression or treatment discontinuation *for a maximum of 24 months of treatment*.
  - Participants with SQ NSCLC will receive blinded pembrolizumab in combination with paclitaxel and carboplatin, all on Day 1 Q3W for four 21-day cycles, followed by blinded pembrolizumab (on Day 1) Q3W until disease progression or treatment discontinuation *for a maximum of 24 months of treatment*.

An overview of the study is presented in Figure 1. The schedule of activities is provided in Section 1.3, Table 1. [redacted]

The study will consist of three phases: screening, treatment, and follow-up.

4.2.1 Screening Phase

After providing informed consent, patients will be evaluated for study eligibility during a 28-day screening period (Days −28 to −1), as presented in the schedule of activities (see Section 1.3, Table 1). Patients who are determined to be eligible on the basis of screening assessments will be randomized to study treatment.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per patient) at the investigator's discretion. Patients are required to re-sign the Informed Consent Form if they are re-screened. For patients who are re-screened, all eligibility criteria must be re-evaluated and the screening assessment should be repeated as applicable to meet

the eligibility criteria. The investigator will maintain a record of reasons for screen failure.

Patients whose tumors have a known *EGFR* mutation or *ALK* genetic aberrations will be excluded from the study. Patients with tumors of non-squamous histology with unknown *EGFR* or *ALK* mutational status will be required to be tested (by local or central testing with a validated health authority approved test or CE-marked test in the European Union per the assay's intended use according to local laws and regulations) prior to enrollment. Patients with tumors of squamous histology who have an unknown *EGFR* or *ALK* mutational status will not be required to be tested at pre-screening/screening.

4.2.2 Treatment Phase

Approximately 180 participants will be randomly assigned to each treatment arm in a 1:1 ratio, enrolling approximately 90 participants per Arm. The study treatment regimens and instructions for administration are presented in Section 6.1.

[redacted]

- [redacted]
- [redacted]
- [redacted]

For additional details on treatment assignment and blinding, refer to Section 6.3.

[redacted]

4.2.3 Safety Run-In Evaluation

An initial safety run-in evaluation will be implemented to assess the safety and tolerability of the novel combination of blinded tobemstomig and chemotherapy. During the safety run-in evaluation, a minimum of [redacted] participants with NSCLC of each histology (SQ and NSQ) are required. This would comprise a minimum of [redacted] participants per histology per arm, corresponding to a total of approximately [redacted] participants. These participants will be evaluated for safety after they have had the opportunity to complete

two cycles of treatment. Participants from each [redacted] patient group who withdraw from treatment before completing two cycles of treatment will also be included in the safety run-in evaluation. After enrollment of the first [redacted] patients per histology group, randomization will continue but will be temporarily suspended if a cap of [redacted] participants per NSCLC histology (approximately [redacted] participants in Arm A and [redacted] in Arm B) is reached before the safety run-in is cleared by an Internal Monitoring Committee (IMC).

The safety run-in evaluation will be performed by the IMC. The Sponsor may conduct one IMC review per histology or a combined IMC review of data arising from both histologies, according to the recruitment rate per histology. If enrollment of participants with a specific histology is suspended as a result of reaching the [redacted] participant enrollment cap, it will be resumed following the IMC's review, taking into consideration any recommendations from that review. No crossover will be allowed from the control arm to the experimental arms.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

4.2.4 Assessments

Participants will undergo a series of assessments as detailed in the schedule of activities (see Section 1.3, Table 1) [redacted] *As a result of the* [redacted] *the schedule of activities has been changed.*

Tumor assessments will be performed at baseline and every *12* weeks (±7 days) regardless of treatment dose delays, until radiographic disease progression per Response Criteria in Solid Tumors, Version 1.1 (RECIST v1.1; see Appendix 10), withdrawal of consent, study termination by Sponsor, or death, whichever occurs first. Participants who are treated beyond disease progression per RECIST v1.1 will undergo tumor assessments every *12* weeks (±2 weeks) after initial documentation of progression, or more frequently if clinically indicated, regardless of time in the study, until treatment is discontinued.

Participants who discontinue treatment for reasons other than radiographic disease progression per RECIST v1.1 (e.g., toxicity, symptomatic deterioration) will continue scheduled tumor assessments at the same frequency as would have been followed if the participant had continued study treatment (i.e., every *12* weeks [±7 days*],* until radiographic disease progression per RECIST v1.1, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first), regardless of whether the patient starts a new anti-cancer therapy.

Participants randomized into the study will be asked to complete PRO questionnaires (see Section 1.3, Table 1). Item Libraries (ILs) 85, 132, 188, and 17 from the European Organisation for Research and Treatment of Cancer (EORTC) will assess symptoms of lung cancer (i.e., fatigue, cough, chest pain, bone pain, and dyspnea), physical and role functioning, and global HRQoL. Selected items from the National Cancer Institute (NCI) Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) and the EORTC IL46 will focus on presence, frequency of occurrence, severity, and/or degree of interference with daily function and bother of symptomatic treatment toxicities related to treatment with tobemstomig, pembrolizumab, and chemotherapy. *As a result of the* [redacted] *PRO assessments for all remaining patients will no longer be required.*

Safety assessments at study visits will include the incidence, nature, and severity of adverse events, protocol-mandated vital signs, laboratory abnormalities, and other protocol-specified tests that are deemed critical to the safety evaluation of the study. The severity of adverse events will be assessed by investigators according to the NCI Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0), with the exception of CRS; the severity of CRS will be determined according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading Scale (Lee et al. 2019).

During the study, [redacted] (see Section 1.3, Table 2). Participant samples, including archival and fresh tumor tissue, serum, plasma, and blood samples, *were to* be collected for

exploratory biomarker assessments, *but, as a result of the* [redacted] *samples for exploratory biomarker assessments will no longer be collected.*

4.2.5 Treatment Beyond Progression

During the study, participants who meet the criteria for disease progression as assessed by the investigator according to RECIST v1.1 (see Appendix 10) and show evidence of clinical benefit may continue treatment with tobemstomig *or* pembrolizumab *for up to 24 months as part of the study* at the investigator's discretion, provided that participants meet all of the following criteria:

- Evidence of clinical benefit*:*
  - Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcemia]) indicating unequivocal progression of disease
  - Absence of decline in Eastern Cooperative Oncology Group (ECOG) Performance Status that can be attributed to disease progression
  - Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- *The participant must provide* written informed consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial radiographic progression per RECIST v1.1

Investigator assessment of overall tumor response at all timepoints will be based only on RECIST v1.1 (see Appendix 10). However, the size of measurable new lesions will also be captured in the eCRF.

4.2.6 *Safety* Follow-Up Phase

After participants discontinue study treatment*, they* will be followed for *safety for 90 days.*

4.2.7 *Safety Monitoring*

[redacted] *safety will be monitored at regular intervals by the study team.*

4.3 RATIONALE FOR *ORIGINAL* STUDY DESIGN

Lung cancer remains the leading cause of cancer deaths worldwide. In the United States, it was estimated that there were 228,820 new cases of lung cancer in 2019 and 135,720 lung cancer deaths (Siegel et al. 2020). Similar data from Europe estimated that in 2018, there were 387,900 lung cancer deaths (Ferlay et al. 2018). Despite significant advances with combination immunotherapy and the approval of immune CPI agents in combination with chemotherapy as first-line therapy for patients with advanced NSCLC. The majority of patients with advanced NSCLC progress while receiving currently available treatment and ultimately experience disease progression and succumb to this disease. Therefore, a high unmet medical need persists for

patients with advanced NSCLC. To improve treatment outcomes for patients with NSCLC, multiple combinations with anti–PD-1/PD-L1 agents are being assessed (for previous discussion, see Section 2.3).

A detailed description of the chemistry, pharmacology, and safety of tobemstomig is provided in the Tobemstomig Investigator's Brochure.

4.3.1 Rationale for Study Population

This study will enroll previously untreated individuals with locally advanced unresectable (Stage IIIB/IIIC) or metastatic (Stage IV) NSQ or SQ NSCLC who are not eligible for curative surgery and/or definitive chemoradiotherapy. Patients without known *EGFR* or *ALK* genetic aberrations with any level of PD-L1 expression are eligible for enrollment. Patients whose tumors have a known EGFR mutation or ALK genetic aberrations will be excluded from the study. Patients with tumors of non-squamous histology with unknown EGFR or ALK mutational status will be required to be tested (by local or central testing with a validated health authority-approved test or CE-marked test in the EU per the assay's intended use according to local laws and regulations) prior to enrollment. Patients with tumors of squamous histology who have an unknown EGFR or ALK mutational status will not be required to be tested at pre-screening/screening.

Expression of LAG3 has been reported across various tumor types, including breast, ovarian, NSCLC, melanoma, renal, and prostate (Matsuzaki et al. 2010; Baitsch et al. 2011; Thommen et al. 2015; He et al. 2016; Norström et al. 2016). LAG3 is frequently co-expressed with PD-1 on TILs, and dual blockade of PD-1 and LAG3 has been shown to enhance $CD8^+$ T-cell–effector function and potentiate anti-tumor immunity in preclinical mouse models. Given the available extensive clinical data and approval of CPI agents (alone or in combination with chemotherapy) for the treatment of patients with NSCLC in the first-line setting, tobemstomig with its blocking action of both PD-1 and LAG3 is hypothesized to generate additional benefit over the combination containing only a PD-1 CPI and in a broad NSCLC patient population.

4.3.2 Rationale for Testing Tobemstomig in Combination with Platinum-Based Chemotherapy in Participants with NSCLC across All PD-L1 Expression Subgroups and Histologies

Several Phase III studies (Gandhi et al. 2018; Paz-Ares et al. 2018; Socinski et al. 2018; West et al. 2019) have demonstrated the benefit of immunotherapy combined with chemotherapy in patients with NSQ NSCLC regardless of PD-L1 expression. This Phase II study design is based on the hypothesis that tobemstomig in combination with platinum-based chemotherapy may improve overall ORR and prolong progression-free survival (PFS) compared with pembrolizumab plus platinum-based chemotherapy in patients with NSCLC in the first-line setting.

4.3.3 Rationale for Control Arm

The current NCCN and European Society of Medical Oncology (ESMO) guidelines for the first-line treatment of NSCLC include pembrolizumab in combination with platinum-based chemotherapy (regardless of PD-1 status) or pembrolizumab as a single agent for patients with high PD-1 expression (TPS ≥50%) (ESMO 2019; NCCN 2019).

In this study, participants with NSQ NSCLC in the control arm will receive four cycles of pembrolizumab in combination with carboplatin and pemetrexed, followed by pembrolizumab plus pemetrexed until disease progression per investigator-assessed RECIST v1.1. Participants with SQ NSCLC will receive four cycles of pembrolizumab in combination with carboplatin and paclitaxel, followed by pembrolizumab until disease progression per RECIST v1.1. The treatments selected for the control arm are approved options for the first-line treatment of patients with NSCLC.

4.3.4 Rationale for Blinding

Platinum-based chemotherapy in combination with pembrolizumab is an established standard of care for a large proportion of patients with locally advanced or metastatic NSCLC. In order to reduce any potential bias toward one or the other treatment combination, either by participants or investigators, blinding will be implemented (refer to Section 6.3.2 for details).

[redacted]

4.3.6 Rationale for Exclusion of Patients with an *EGFR* Mutation or *ALK* Rearrangements

Patients with tumors harboring an *EGFR* mutation or *ALK* rearrangements are not eligible for enrollment in this study. Genotype-directed therapy, rather than immunotherapy, remains the standard of care in the first-line treatment setting for such patients.

4.3.7 Rationale for Confirmed Objective Response Rate and Progression-Free Survival as Primary Endpoints

Confirmed ORR is a common primary endpoint in proof-of-concept Phase II studies given its usefulness as an early indicator of clinical activity (Food and Drug Administration [FDA] 2007; European Medicines Agency [EMA] 2012).
Although confirmed ORR can reflect tumor growth and can be assessed earlier and with a smaller sample size compared with survival studies, confirmed ORR may not always correlate with survival.

PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit. In addition, its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit–risk profile of the new treatment compared with available therapies (EMA 2012; FDA 2018).

[redacted]

4.3.9 *Rationale for Collection of Information on Race and Ethnicity*

Data pertaining to participant race and ethnicity represents a component of the broad demographic profile of the study population. Collection of demographic data, including information on race and ethnicity, is of importance to the future interpretation of results from the clinical trial, including identification of potential differences in efficacy, safety, and pharmacokinetics among participants. Collection of race and ethnicity data may enable investigation of potential relationships between biomarkers and race or ethnicity, including determination of whether race or ethnicity could be a prognostic factor. Collection of these data may also contribute to a better understanding of the distribution of NSCLC according to race or ethnicity.

4.3.10 Rationale for Exploratory Safety Biomarker Assessments

Tobemstomig is a novel IgG1-based BsAb that targets the checkpoint receptors PD-1 and LAG3 on immune effector cells, particularly T cells, with the aim to reinvigorate T cells. The costimulatory action of tobemstomig on PD-1 and LAG3 receptors might bear the risk of exaggerated immune cell activation, particularly given LAG3 modulation. This may result in the occurrence of enhanced or untoward immune-mediated adverse events. Immune-mediated adverse events can involve any organ or tissue, although some events occur much more frequently than others (for details, refer to the Tobemstomig Investigator's Brochure).

The mechanisms that result in immune-mediated adverse events with CPI therapies are still being elucidated and are likely to be multifactorial (e.g., increasing T-cell activity against antigens that are present in tumors and healthy tissue, expansion of T cell–receptor diversity and expansion of T-cell clones, increased levels of pre-existing autoantibodies, and an increase in the level of inflammatory cytokines (Sullivan et al. 2018). Understanding the mechanisms of such side effects and how they can be used to distinguish between the anti-tumor effects of CPI agents, as well as to identify biomarkers that may be predictive of development of immune-related toxicities, will facilitate the conduct of trials to limit their onset and improve patient outcomes (Friedman and Postow 2016).

In this study, exploratory research on safety biomarkers may be conducted to support future drug development and to understand the mechanistic basis of immune-mediated adverse events. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. The samples for assessment are presented in Section 8.7 and may be used for this exploratory research. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not be used to inform decisions on patient management.

4.3.11 Rationale for Exploratory Biomarker Assessments

Exploratory biomarker analysis will be performed in an effort to understand the association of such markers with study treatment response, efficacy (including pathological response), and/or adverse events. The tumor biomarkers from tissue and blood samples include, but are not limited to, PD-L1, CD-8, LAG3, tumor mutational burden, and circulating tumor DNA. Methods for assessment include, but are not limited to, IHC, gene expression, etc.

4.3.12 Rationale for Whole Genome and Whole Exome Sequencing

Blood samples *that were* collected for DNA extraction *under previous versions of the protocol may be used* to enable whole genome sequencing (WGS) or whole exome

sequencing (WES) with a special focus on germline to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or that may be predictive of which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development. In this study, blood samples *that have been* obtained *under previous versions of this protocol may be* submitted for WGS or WES and *are* contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body (see Section 8.10.3.2).

4.3.13 Rationale for Patient-Reported Outcome Assessments

In the treatment of lung cancer, it is important to increase both survival and palliate symptoms since disease symptoms negatively impact HRQoL (Hyde and Hyde 1974; Hopwood and Stephens 1995; Sarna et al. 2004). This is especially true for studies that have ORR and PFS as primary endpoints to inform how delays in radiographic progression might be associated with delays in clinical progression of symptoms and their interference with role and physical functioning, including maintaining low disease burden. As such, validated PRO questionnaires have been incorporated in this study to assess symptom severity and symptom impact on functioning, including HRQoL and treatment tolerability, as assessed by the EORTC ILs (see Appendix 7).

Cancer treatments, particularly combination therapies, can produce significant symptomatic adverse events. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch 2010; Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting adverse event information directly from participants can improve the understanding of treatment characteristics and their effects. In order to evaluate the tolerability of tobemstomig, pembrolizumab, and platinum-based chemotherapy participants will be asked to report on their experience related to decreased appetite, nausea, vomiting, diarrhea, rash, hair loss, itching and joint pain, treatment-related symptoms selected from the validated PRO-CTCAE item bank (see Appendix 7). Such symptoms were identified as being salient to patients' experience with tobemstomig, pembrolizumab, and platinum-based chemotherapy based on their license agreements.

Data generated from these PRO questionnaires will inform patients' experience with disease burden and treatment tolerability as part of the totality of evidence generated to inform the benefit–risk profile of tobemstomig.

4.4 JUSTIFICATION FOR [redacted]*MG* DOSE AND SCHEDULE

[redacted]

4.5 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including the last visit/last scheduled procedure specified in the schedule of activities (see Section 1.3, Table 1).

The end of this study is defined as the date of the last visit of the last participant in the study. The end of the study is expected to occur *no later than 28* months after the last participant is enrolled*, which includes screening, up to 2 years of study treatment, and 90 days of safety follow-up after the last dose of study treatment*.

In addition, the Sponsor may decide to terminate the study at any time.

4.6 DURATION OF PARTICIPATION

Treatment will continue until disease progression per RECIST v1.1, unacceptable toxicity, *or* loss of clinical benefit as determined by the investigator (see Section 7.1 for additional details), *up to 24 months,* or until the Sponsor decides to terminate the study, whichever comes first. The total duration of study participation for each individual is expected to range from 1 day to approximately *28* months. Participants will be allowed

to continue treatment beyond disease progression *for up to 24 months if prespecified* criteria are met (Section 4.2.5).

5. STUDY POPULATION

Approximately 180 previously untreated participants with locally advanced, unresectable metastatic NSCLC of SQ or NSQ histology who are not eligible for curative surgery or definitive chemoradiotherapy, with no *EGFR* mutations or *ALK* genetic aberrations, will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form
- Age ≥18 years at the time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- ECOG Performance Status of 0 or 1 (see Appendix 11)
- Histologically or cytologically documented locally advanced, unresectable (Stage IIIB/IIIC) or metastatic (Stage IV) NSCLC who are not eligible for curative surgery and/or definitive chemoradiotherapy (8th edition of the UICC/AJCC-staging system)

  Patients with NSCLC of mixed histology and patients with small-cell lung cancer are not eligible for enrollment in the study.
- No prior systemic treatment for metastatic NSCLC

  Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a treatment-free interval of at least 12 months from randomization since the last dose of chemotherapy and/or radiotherapy.
- Known tumor PD-L1 status through a documented local assessment using a health authority–approved PD-L1 IHC assay
- Confirmed availability of representative tumor specimens in formalin-fixed, paraffin-embedded (FFPE) blocks (preferred) or 15 (or an absolute minimum of 12) unstained serial slides, along with an associated pathology report

  If central testing for *EGFR* mutations and/or *ALK* rearrangements is required, an additional 5 unstained slides must be provided.

  Tumor tissue should be of good quality based on total and viable tumor content (i.e., a minimum number of 100 viable TCs with preserved cellular context and tissue architecture). Acceptable samples include samples from resections, core-needle biopsies for deep tumor tissue (with a minimum of three cores for

freshly collected biopsies) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions, or endobronchial ultrasound (EBUS) core-needle biopsy.

EBUS-transbronchial needle aspiration is acceptable (particularly if a larger gauge needle is used), provided tissue is of good quality as described above (i.e., a minimum number of 100 viable TCs with preserved cellular context and tissue architecture). For EBUS-needle aspirations, an 18-gauge or larger needle is recommended.

Fine-needle aspirations that do not preserve tissue architecture and yield cell suspension and/or cell smears, brushings, cell pellets from pleural effusions, and lavage samples are not acceptable.

Tumor tissue from bone metastases is not evaluable for tumor PD-L1 expression by immunohistochemistry and is therefore not acceptable.

If archival tissue is either insufficient or unavailable, the patient may undergo a biopsy at screening if the biopsy site is safely accessible. If collection of a fresh biopsy is not medically feasible, the patient will be eligible if a minimum of 12 unstained, serial slides can be provided. If central testing for *EGFR* mutations and/or *ALK* rearrangements are required, an additional 5 unstained slides must be submitted.

- Measurable disease, as defined by RECIST v1.1 (see Appendix 10)

  Previously irradiated lesions can only be considered measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of measurable disease.

- Life expectancy ≥ 12 weeks

- Adequate hematologic and end-organ function, as defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1):

  – ANC $\geq 1.5 \times 10^9$/L ($\geq 1500/\mu$L) without granulocyte colony-stimulating factor support with the following exception: Patients with benign ethnic neutropenia (BEN) and ANC $\geq 1.3 \times 10^9$/L ($\geq 1300/\mu$L) are eligible.

    BEN (also known as constitutional neutropenia) is an inherited cause of mild or moderate neutropenia that is not associated with any increased risk for infections or other clinical manifestations (Atallah-Yunes et al. 2019). BEN is referred to as ethnic neutropenia because of its increased prevalence in people of African descent and other specific ethnic groups.

  – Lymphocyte count $\geq 0.5 \times 10^9$/L ($\geq 500/\mu$L)

  – Platelet count $\geq 100 \times 10^9$/L ($\geq 100{,}000/\mu$L) without transfusion

  – Hemoglobin ≥ 90 g/L (≥ 9 g/dL)

    Patients may be transfused or receive erythropoietic treatment as per local standard of care to meet this criterion.

  - AST, ALT, and ALP $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Total bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN
  - Creatinine clearance (CrCl) ≥ 45 mL/min, calculated with use of the Cockcroft-Gault formula (Cockcroft and Gault 1976; see Section 6.1.2) or by 24-hour urine collection for determination of CrCl
  - Albumin ≥ 25 g/L (≥ 2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR and aPTT $\leq 1.5 \times$ ULN

    For patients receiving therapeutic anticoagulation: stable anticoagulant regimen
- Negative HIV test at screening, with the following exception:

  Individuals with a positive HIV test at screening are eligible, provided they are stable on anti-retroviral therapy, have a CD4 count $\geq 200/\mu$L, and have an undetectable viral load.
- Negative hepatitis B surface antigen test at screening
- Positive hepatitis B surface antibody (HBsAb) test at screening, or negative HBsAb at screening accompanied by either of the following:
  - Negative total hepatitis B core antibody (HBcAb)
  - Positive total HBcAb test followed by a negative (per local laboratory definition) hepatitis B virus (HBV) DNA test
  - The HBV DNA test must be performed for individuals who have a negative HBsAg test, a negative HBsAb test, and a positive HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Adequate cardiovascular function, as evidenced by the following:
  - New York Heart Association Heart Failure Class II or less
  - Baseline-corrected QT (through use of Fridericia's formula [QTcF]) interval ≤ 480 ms

    If the QTcF interval is longer than 480 ms but is shorter than 500 ms, the patient may undergo a cardiac evaluation and will be considered for treatment in case of no clinically significant findings.

  - Resting systolic blood pressure $\leq$150 mmHg and diastolic blood pressure $\leq$100 mmHg (average of three or more readings during two or more sessions with a short break between sessions) or no clinically significant hypertension
  - Resting heart rate between 45 and 100 bpm (or no clinically significant tachycardia)
  - Left ventricular ejection fraction $\geq$50%, as assessed by either transthoracic echocardiogram (TTE) or multiple-gated acquisition (MUGA) scan (TTE preferred test) within 6 months prior to initiation of study treatment
- For female participants of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Female participants must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for 4 months after the final dose of tobemstomig, 4 months after the final dose of pembrolizumab, and 6 months after the final dose of platinum-based chemotherapy. Women must refrain from donating eggs during this same period.

  A female participant is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause, as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $<$1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

  Women who would like to become pregnant after discontinuation of study treatment should seek advice about oocyte preservation prior to initiation of study treatment because of the possibility of irreversible infertility due to treatment with carboplatin.

- For male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for 4 months after the final dose of tobemstomig, 4 months after the final dose of pembrolizumab, *3 months after the final dose of pemetrexed,* and 6 months after the final dose of paclitaxel and carboplatin. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 4 months after the final dose of tobemstomig, 4 months after the final dose of pembrolizumab, *3 months after the final dose of pemetrexed,* and 6 months after the final dose of paclitaxel and carboplatin to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

  Men who would like to father a child after initiation of study treatment should seek advice about sperm preservation prior to initiation of study treatment because of the possibility of irreversible infertility due to treatment with pemetrexed or carboplatin.

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- NSCLC known to have a mutation in the *EGFR* gene or an *ALK* fusion oncogene

  Patients with tumors of non-squamous histology with unknown *EGFR* or *ALK* mutational status will be required to be tested (by local or central testing with a validated health authority approved test or CE-marked test in the EU per the assay's intended use according to local laws and regulations) prior to enrollment. Patients with tumors of squamous histology who have an unknown *EGFR* or *ALK* mutational status will not be required to be tested at pre-screening/screening.

  EGFR and/or *ALK* status may be assessed locally or at a central laboratory.

  EGFR status assessed locally must be performed on tissue with use of a test that detects mutations in Exons 18–21.

  EGFR and/or *ALK* testing should be performed with a validated, health authority–approved test (i.e., commercially available test approved by your country or local government), and sample requirements and testing must be

performed per the assay's intended use and according to the assay manufacturer's specifications. If *EGFR* and/or *ALK t*esting does not meet these criteria, *EGFR* and/or *ALK* must be assessed centrally.

If samples are submitted for central *EGFR* and/or *ALK* testing, an additional 5 slides must be provided.

- Symptomatic, untreated, or actively progressing CNS metastases

  Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:

  – Measurable disease, per RECIST v1.1, must be present outside the CNS.

  – The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.

  – The patient has not undergone stereotactic radiotherapy within 7 days prior to randomization, whole-brain radiotherapy within 14 days prior to randomization, or neurosurgical resection within 28 days prior to randomization.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease.

  – If the patient is receiving anti-convulsant therapy, the dose is considered stable.

  – Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).

  – There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment.

  – There is no evidence of significant vasogenic edema.

  Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.

- Spinal cord compression not definitively treated with surgery and/or radiation or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for $\geq$2 weeks prior to initiation of study treatment
- History of leptomeningeal disease
- Uncontrolled tumor-related pain

  – Patients requiring pain medication must be on a stable regimen at study entry.

  – Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should be treated prior to initiation of study treatment. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  – Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not

currently associated with spinal cord compression) should be considered for locoregional therapy, if appropriate, prior to enrollment.

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once a month or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL, or corrected calcium greater than ULN)
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, granulomatosis with polyangiitis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 8) with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  – Rash must cover < 10% of body surface area
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  – No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on the screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Active tuberculosis (TB), as documented by a positive purified protein derivative (PPD) skin test or TB blood test and confirmed by a positive chest X-ray within 3 months prior to initiation of study treatment

  Patients with a positive PPD skin test or TB blood test followed by a negative chest X-ray may be eligible for the study.

- Untreated latent TB
- Current treatment with anti-viral therapy for HBV or HCV

- Significant cardiovascular disease within 3 months prior to randomization, including any of the following:
  - Hypertensive crisis or encephalopathy
  - Unstable angina
  - Transient ischemic attack or stroke
  - Congestive heart failure (according to the New York Heart Association classification, refer to the inclusion criteria in Section 5.1)
  - Serious cardiac arrhythmia requiring treatment (exceptions are atrial fibrillation, paroxysmal supraventricular tachycardia)
  - History of thromboembolic events (such as myocardial infarction, stroke, or pulmonary embolism)
  - Troponin T (TnT) or troponin I (TnI) greater than or equal to the institutional ULN

    Patients with TnT or TnI levels between >1 and $<2\times$ ULN will be permitted to enroll in the study if repeat levels are $\leq 1\times$ ULN. If repeat levels are between >1 and $<2\times$ ULN, the patient may undergo a cardiac evaluation and will be considered for treatment in case of no clinically significant findings.
- Major surgical procedure, other than for diagnosis, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study
- History of malignancy other than NSCLC within 5 years prior to randomization, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS] rate $>90\%$), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal breast carcinoma in situ, or Stage I uterine cancer
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that could affect patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Prior allogeneic stem cell or solid organ transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high-risk from treatment complications
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment or within 5 months after the final dose of study treatment

- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Any anti-cancer therapy, including hormonal therapy, within 21 days prior to initiation of study treatment
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including, but not limited to, anti-cytotoxic T lymphocyte–associated protein 4, anti–T-cell immunoreceptor with Ig and tyrosine-based inhibition motif domains, anti–PD-1 and anti–PD-L1 therapeutic antibodies, and anti-LAG3) agents
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment

Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:

  – Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
  – Patients who received mineralocorticoids (e.g., fludrocortisone), inhaled or low-dose corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies, fusion proteins, or platinum-containing compounds
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the tobemstomig or pembrolizumab formulation
- Known allergy or hypersensitivity or other contraindication to any component of the chemotherapy regimen the patient may receive during the study
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study, within 4 months after the final dose of tobemstomig and pembrolizumab, or 6 months after the final dose of paclitaxel, pemetrexed, or carboplatin

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

- Known targetable c-*ROS1, BRAF*^{V600E} or *RET* proto-oncogene genomic aberrations

  Patients with known targetable *ROS1*, *BRAF*^{V600E} or *RET* genomic aberrations are permitted for trial enrollment only if they are ineligible to receive available targeted therapy.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

This study has no caffeine, alcohol, or tobacco restrictions.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion. Individuals must re-sign the consent form prior to re-screening. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

The investigational medicinal products (IMPs) for this study are tobemstomig, pembrolizumab, carboplatin, pemetrexed, and paclitaxel.

6.1 STUDY TREATMENT ADMINISTERED

A description of assigned study treatments for this study is presented in Table 5.

Table 5 Study Treatment Description

	Tobemstomig	Pembrolizumab	Paclitaxel	Carboplatin	Pemetrexed
Use	Experimental	Comparator	Experimental	Experimental	Experimental
Type of medicinal product	Roche IMP	Non-Roche IMP	Non-Roche IMP	Non-Roche IMP	Non-Roche IMP
Drug form	Liquid	Concentrate solution for IV infusion	Concentrate solution for IV infusion	Concentrate solution for IV infusion	Powder for concentrate solution for IV infusion
Unit dose strength	[redacted] mg per vial	100 mg/4 mL per vial	6 mg/mL	10 mg/mL	500 mg per vial
Dosage level	[redacted] mg Q3W	200 mg Q3W	200 mg/m^2 Q3W	AUC 5 mg/mL • min Q3W	500 mg/m^2 Q3W
Formulation	Refer to pharmacy manual and Tobemstomig Investigator's Brochure.	Refer to pembrolizumab USPI or SmPC.	Refer to paclitaxel USPI or SmPC	Refer to carboplatin USPI or SmPC.	Refer to pemetrexed USPI or SmPC.
Packaging	[redacted]	10-mL vial	100 and 150 mg vials	450 mg vials	500 mg/vial
Labeling	Per local requirement	Per local requirements	Per local requirements	Per local requirements	Per local requirements
Route of administration	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion
Source	Sponsor	Sponsor	Sponsor	Sponsor	Sponsor

AUC = area under the concentration–time curve; IMP = investigational medicinal product; Q3W = every 3 weeks; SmPC = Summary of Product Characteristics; USPI = U.S. Package Insert.

In this protocol, "study treatment" refers to the following combination of treatments assigned to participants in Arm A or Arm B as part of this study:

- Arm A
  - For patients with NSQ NSCLC, induction treatment with blinded tobemstomig in combination with pemetrexed and carboplatin Q3W for four cycles, followed by Q3W maintenance therapy with blinded tobemstomig in combination with pemetrexed Q3W
  - For patients SQ NSCLC, blinded tobemstomig in combination with paclitaxel and carboplatin Q3W for four cycles, followed by blinded treatment with tobemstomig Q3W
- Arm B
  - For patients with NSQ NSCLC, induction treatment with blinded pembrolizumab in combination with pemetrexed and carboplatin Q3W for four cycles, followed by maintenance therapy with blinded pembrolizumab in combination with pemetrexed Q3W
  - For patients with SQ NSCLC, blinded treatment with pembrolizumab in combination with paclitaxel and carboplatin Q3W for four cycles, followed by blinded pembrolizumab Q3W

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 6.

The induction phase of the study will consist of 4 cycles of blinded tobemstomig or pembrolizumab plus histology-based chemotherapy. On Day 1 of each cycle, all eligible patients will be administered study drug infusions in the following order:

- *Arm A NSQ: blinded tobemstomig → pemetrexed → carboplatin*
- *Arm A SQ: blinded tobemstomig → paclitaxel → carboplatin*
- *Arm B NSQ: blinded pembrolizumab → pemetrexed → carboplatin*
- *Arm B SQ: blinded pembrolizumab → paclitaxel → carboplatin*

6.1.1 Blinded Tobemstomig and Blinded Pembrolizumab

Participants will receive blinded tobemstomig ([redacted] mg Q3W) or blinded pembrolizumab (200 mg Q3W) by IV infusion. Administration of study treatment will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. The [redacted]-mg dose of tobemstomig Q3W and the 200-mg dose of pembrolizumab Q3W will remain the same throughout the study.

The initial dose of tobemstomig or pembrolizumab will be delivered over [redacted] minutes by IV infusion. If the [redacted]-minute infusion is tolerated without infusion-associated adverse events (fever or chills), the second infusion may be delivered over [redacted]

minutes. If the [redacted]-minute infusion is well tolerated, all subsequent infusions may be delivered over [redacted] minutes.

Participants who experience an infusion-associated adverse event may be premedicated with an antihistamine and/or antipyretic medication for subsequent doses and beyond at the discretion of the investigator, but the infusion time may not be decreased for that infusion.

Tobemstomig and pembrolizumab infusions will be administered to participants per the instructions outlined in Table 6.

Table 6 Administration of First and Subsequent Infusions of Tobemstomig or Pembrolizumab

Study Drug	First Infusion	Subsequent Infusions
Tobemstomig or pembrolizumab infusion	• No premedication is permitted for the first infusion of tobemstomig and pembrolizumab. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to starting the infusion. • Tobemstomig and pembrolizumab should be infused over [redacted] minutes. • If clinically indicated, vital signs should be recorded every 15 (±5) minutes during the infusion.	• If the patient experienced an IRR with any previous infusion of tobemstomig or pembrolizumab, premedication with an antihistamine and/or antipyretic may be administered for subsequent doses and beyond at the discretion of the investigator. • Vital signs should be recorded within 60 minutes prior to the infusion. • Tobemstomig and pembrolizumab should be infused over [redacted] minutes if the previous infusion was tolerated without an IRR o [redacted] minutes if the patient experienced an IRR with the previous infusion. • If clinically indicated, vital signs should be recorded during the infusion.
Observation period after tobemstomig or pembrolizumab infusion	• After the infusion of tobemstomig or pembrolizumab, the patient begins a [redacted]-minute observation period. • Vital signs should be recorded at 30 (±10) minutes after the infusion of tobemstomig or pembrolizumab. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient tolerated the previous tobemstomig or pembrolizumab infusion well without infusion-associated adverse events, the observation period after the next and following infusions may be reduced to [redacted] minutes. • If the patient experienced infusion-associated adverse events in the previous infusion, the observation period should be [redacted] minutes. • If clinically indicated, vital signs should be recorded at 30 (±10) minutes after the infusion of tobemstomig or pembrolizumab.

IRR = infusion-related reaction.

6.1.2 Paclitaxel, Pemetrexed, and Carboplatin

Paclitaxel

Paclitaxel 200 mg/m^2 will be administered as an IV infusion to participants over 3 hours Q3W for four cycles as per local practice and labels. All participants should be premedicated with oral or an IV steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be

administered as per standard practice. Paclitaxel should be completely administered before initiating carboplatin dose.

Pemetrexed

Pemetrexed 500 mg/m^2 will be administered to participants as an IV infusion over 10 minutes Q3W until progression or unacceptable toxicity.

All participants should receive the appropriate supplementation with vitamin B12, folic acid, and corticosteroid prophylaxis as listed below (or as per local label):

- Folic acid 350–1000 μg orally (PO): Participants must take at least five doses of folic acid 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 final dose of pemetrexed.
- Vitamin B12 1000 μg intramuscular (IM) injection: Participants will receive an IM injection the week preceding the first dose of pemetrexed and once every three cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Anti-emetic prophylaxis with dexamethasone 4 mg (or equivalent) PO twice per day: Participants should take dexamethasone the day before, the day of, and the day after pemetrexed administration. Higher or additional doses are permitted for anti-emetic prophylaxis during Cycles 1–4 but not to exceed doses per the Multinational Association of Supportive Care (MASCC) and ESMO guidelines (Roila et al. 2016).

Carboplatin

Carboplatin AUC 5 mg/mL • min: Participants will receive carboplatin as an IV infusion over 30–60 minutes Q3W for four cycles immediately after paclitaxel or pemetrexed as per local practice and labels. The dose of carboplatin should be calculated using Calvert formula (see below) and should not exceed 750 mg.

Calvert Formula:

$$\text{Total dose (in mg)} = (\text{target AUC}) \times (\text{CrCl} + 25).$$

The estimated glomerular filtration rate used in the Calvert formula should not exceed 125 mL/min.

$$\text{Maximum carboplatin dose (mg)} = \text{target AUC}$$
$$5\ (\text{mg/mL} \bullet \text{min}) \times (125 + 25) = 5 \times 150\ \text{mL/min} = 750\ \text{mg}.$$

Paclitaxel, pemetrexed, and carboplatin will be administered to participants as outlined in Table 7.

Table 7 Treatment Regimen for Pemetrexed, Paclitaxel, and Carboplatin

Study Treatment	Dose and Route of Administration	Induction Period (Four 21-Day Cycles)	Maintenance (until PD)
Pemetrexed	500 mg/m^2 by IV infusion	Over approximately 10 minutes on Day 1 Q3W	Over approximately 10 minutes on Day 1 Q3W
Paclitaxel	200 mg/m^2 by IV infusion	Over approximately 3 hours on Day 1 Q3W	Not applicable
Carboplatin	AUC 5 mg/mL • min by IV infusion	Over approximately 30–60 minutes on Day 1 Q3W	Not applicable

AUC = area under the concentration–time curve; PD = progressive disease; Q3W = every 3 weeks.

Details regarding dose modification of paclitaxel, pemetrexed, and carboplatin are presented in Section A4–6.4.2.

Guidelines for medical management of IRRs are provided in the Appendix 6.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, through an interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate

documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and the Tobemstomig and Pembrolizumab Investigator's Brochures or local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT AND BLINDING

6.3.1 Treatment Assignment

This is a randomized, double-blind study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's identification number and treatment assignment through the IxRS.

Participants will be randomly assigned to one of two treatment arms: Arm A (tobemstomig in combination with platinum-based chemotherapy) or Arm B (pembrolizumab in combination with platinum-based chemotherapy). [redacted]

[redacted]

Patients should receive their first dose of study drug on the day of randomization if possible. If this is not possible, the first dose should occur within 5 days after randomization.

[redacted] *treatment beyond 24 months is no longer permitted in either treatment arm. Patients who are continuing treatment beyond 24 months must discontinue from the study and seek other treatment options outside of the study.*

6.3.2 Blinding

Originally, study site personnel (with the exception of the [redacted] pharmacist or equivalent) and participants *were* blinded to treatment assignment during the study.

[redacted].

6.4 STUDY TREATMENT COMPLIANCE

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed.

When participants are treated at the site, they will receive study treatment directly from the investigator or designee under medical supervision.

Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section A3–7.12.

6.5 DOSE MODIFICATION

Dose modifications of tobemstomig, including dose reductions, will not be allowed in this study.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

Currently, the sponsor does not have any plans to *provide* tobemstomig *or any other study treatments* to participants *who have completed the study. The Sponsor may evaluate whether to continue providing tobemstomig* in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, *available at the following website:*

https://assets.cwp.roche.com/f/176343/x/92d6b13ee6/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. Cases of overdose, along with any associated adverse events, should be reported as described in Section A3–7.12.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.

2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until study treatment can no longer be detected systemically (at least 90 days).

6.8 CONCOMITANT THERAPY

Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to initiation of study treatment to the treatment discontinuation visit must be recorded on the Concomitant Medications eCRF along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Permitted Therapy

Use of the following concomitant therapies is permitted as described below:

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 5.1)
- Hormone replacement therapy
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  In participants without documentation of radiographic disease progression, it is strongly encouraged to maximize supportive care for symptomatic management and to avoid radiotherapy that will interfere with the assessment of tumor target lesions. Treatment with tobemstomig and pembrolizumab may be continued during palliative radiotherapy.
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section 6.8.3).
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled or low-dose corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose mineralocorticoids administered for orthostatic hypotension or low-dose mineralocorticoids and corticosteroids for adrenocortical insufficiency

Premedication for pemetrexed, paclitaxel, and carboplatin is permitted. Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered for

the second and subsequent tobemstomig and pembrolizumab infusion only, at the discretion of the investigator.

In general, investigators should manage a participant's care with supportive therapies other than those defined as cautionary or prohibited therapies as clinically indicated, per local standard practice. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

Participants must abstain from taking prescription and non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 drug-elimination half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator after consulting the Medical Monitor, the medication will not interfere with the study.

6.8.2 Cautionary Therapy

6.8.2.1 Corticosteroids, Immunosuppressive Medications, and Tumor Necrosis Factor Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may attenuate potential beneficial immunologic effects of treatment with tobemstomig and/or pembrolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with tobemstomig and pembrolizumab therapy.

6.8.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 6.8.1) may be used during the study at the discretion of the investigator.

6.8.2.3 Other Cautionary Therapy

For information regarding medications that should be used with caution in combination with pemetrexed, paclitaxel, and carboplatin, please refer to the local prescribing information.

6.8.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Investigational therapy (other than protocol-mandated study treatment) within 28 days prior to initiation of study treatment and during study treatment
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority approved or experimental, for various time periods prior to starting study treatment, depending on the agent (see Section 5.2), and during study treatment, until disease progression is documented and the participant has discontinued study treatment, with the exception of palliative radiotherapy, radiotherapy to the brain, and local therapy under certain circumstances (see Section 6.8.1 for details)
- Live, attenuated vaccines within 4 weeks prior to initiation of study treatment, during study treatment, and for 5 months after the final dose of study treatment
- Systemic immunomodulatory agents (including, but not limited to, interferons and interleukin-2) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with study treatment

For information regarding medications that are contraindicated with pemetrexed, paclitaxel, and carboplatin, please refer to the local prescribing information.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Section A1–9.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. Refer to the schedule of activities (see Section 1.3, Table 1) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable

given the individual participant's potential response to therapy and severity of the event

- Any medical condition that the investigator determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Use of a non–protocol-specified anti-cancer therapy
- Symptomatic deterioration attributed to disease progression
- Radiographic disease progression per RECIST v1.1 (unless study treatment is continued beyond radiographic progression)
- For participants treated beyond radiographic disease progression per RECIST v1.1, loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) (see Section 4.2.5 for details)
- *24 months have elapsed from the start of study treatment*

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants will return to the clinic for a treatment discontinuation visit ≤30 days after the final dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Participants who discontinue study treatment for any reason other than progressive disease per RECIST v1.1 will continue to undergo tumor response assessments

Refer to the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3, Table 1). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic and determine if there are ways to support patient participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

Note: Before a participant is deemed lost to follow-up, the site should attempt three telephone calls to the participant and, if necessary, send a certified letter to the participant's last known mailing address or local equivalent methods when possible.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3, Table 1). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., complete blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities (see Section 1.3, Table 1).

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history and use of drugs of abuse will be recorded at screening. Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) and vaccines used by the participant within 7 days prior to initiation of study treatment will be recorded. Demographics, including age, sex, and self-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable.

8.1 EFFICACY ASSESSMENTS

8.1.1 Tumor and Response Evaluations

Participants will undergo tumor assessments every *12* weeks (±7 days*),* regardless of dose delays until radiographic disease progression per RECIST v1.1 (see Appendix 10) or loss of clinical benefit (for participants who continue treatment after radiographic treatment progression), as determined by the investigator, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Participants who are treated beyond disease progression per investigator-assessed RECIST v1.1 will undergo tumor assessments every *12* weeks (±2 weeks) after initial documentation of progression, or more frequently if clinically indicated, regardless of time in the study until treatment is discontinued (see Section 4.2.5 for details). At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. Participants who discontinue study treatment (for any reason, including, but not limited to, clinical decline or toxicity) in the absence of radiographic disease progression per investigator-assessed RECIST v1.1 will *be followed for safety for 90 days after last dose of study treatment.*

All measurable and/or evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening, so long as they meet criteria outlined below.

8.1.1.1 Radiographic Assessments

Screening and subsequent tumor assessments must include CT scans of the chest and abdomen with contrast (per institutional standard operating procedures). A CT scan with contrast of the pelvis is required at screening and as clinically indicated or as per local standard of care at subsequent response evaluations. If a CT scan with contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and magnetic resonance imaging (MRI) scans (with contrast, if feasible) of the abdomen and pelvis should be performed. CT or MRI scans of other disease sites should be performed as clinically indicated.

All participants must undergo an MRI or CT scan (with contrast) of the brain at screening. In the event of an equivocal CT scan at screening, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases. Subsequent brain scans should be performed only if clinically indicated (i.e., if a participant becomes symptomatic). Patients with active or untreated CNS metastases are not eligible for the study (see Section 5.2). At subsequent (post-screening) tumor assessments, participants with a history of irradiated brain metastases at screening are not required to undergo brain scans unless clinically indicated (e.g., in participants with neurologic symptoms); irradiated brain metastases do not need to be categorized and followed as target or non-target lesions at baseline or at subsequent tumor assessments.

At the investigator's discretion, other methods of assessment of disease as per RECIST v1.1 may be used. If a CT scan for tumor assessment is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. Further investigations, such as bone scans and CT scans of the neck, should also be performed if clinically indicated.

All measurable and/or evaluable lesions identified at screening should be re-assessed at subsequent tumor evaluations according to the schedule described above. The same

radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). Tumor assessments must be continued after disease progression per RECIST v1.1 for participants who receive treatment beyond progression. The investigator's assessment of overall tumor response at all timepoints should be based on RECIST v1.1 only. Results must be reviewed by the investigator before dosing at the next cycle.

Radiographic images, whether reviewed locally or centrally, must be evaluated by a qualified, certified expert.

8.1.1.2 Response Evaluation

Objective response will be determined by the investigator at specified timepoints according to RECIST v1.1 (see Appendix 10). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits.

Other endpoints (e.g., PFS, OS, DOR) will be calculated programmatically by the Sponsor on the basis of investigator assessments of response at each specified timepoint.

8.1.2 Clinical Outcome Assessments

PRO questionnaires will be completed to assess the treatment benefit of tobemstomig plus platinum-based chemotherapy. In addition, PRO questionnaires enable the capture of each participant's direct experience with tobemstomig plus platinum-based chemotherapy. PRO data will be collected through use of the following questionnaires: EORTC IL85, IL132, IL188, and IL17.

The order of administration for the PRO*s* is outlined in the schedule of activities (see Section 1.3, Table 1). [redacted], *PRO questionnaires for participants continuing in the study will no longer be required.*

8.1.2.1 Data Collection Methods for Clinical Outcome Assessments [redacted]

The PRO questionnaires, translated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study (see Section 1.3, Table 1). Paper versions of the PRO questionnaires will be self-administered by participants during the treatment period and site personnel will administer the NCI PRO-CTCAE and EORTC IL46 to participants over the telephone at the Day 8 visit, at follow-up visits, and in exceptional circumstances if a participant cannot attend a site visit. Source documentation should be obtained that includes, among other information, that the questionnaires were administered by telephone. Site personnel will enter PRO data on the eCRF.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be

completed in their entirety by the participant prior to receiving any information on disease status, and prior to the administration of study treatment, unless otherwise specified (see Section 1.3, Table 1).

8.1.2.2 EORTC Item Libraries 85, 132, 188, and 17

The IL85 is composed of five lung cancer–specific items from the EORTC, assessing cough, shortness of breath, and chest pain (see Section A7–1.1.1). The IL85 takes approximately 3 minutes to complete.

The IL132 consists of three items of relevance to patients with cancer from the EORTC, assessing fatigue (see Section A7–1.1.2). The IL132 takes approximately 2 minutes to complete.

The IL188 is a single-item from the EORTC, evaluating bone pain in patients with cancer (see Section A7–1.1.3). The IL188 takes approximately 1 minute to complete.

The IL17 is composed of nine items of relevance to patients with cancer from the EORTC, assessing physical functioning, role functioning, and GHS/QoL (see Section A7–1.1.4). The IL17 takes approximately 4 minutes to complete.

The recall period for these IL assessments is specified to be during the past week. The administration schedule and requirements are described in Section 1.3, Table 1.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessment of a participant's weight and height, the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

A limited physical examination will include, at a minimum, symptom-directed physical examination. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from abnormalities identified at screening should be recorded in participant notes. After initiation of study treatment, any new or worsened clinically significant abnormalities (i.e., beyond expected variation or normal age-related changes) should be recorded as adverse events on the Adverse Event eCRF.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention).

8.2.2 Vital Signs

Temperature, pulse rate, respiratory rate, and blood pressure will be assessed as specified in the schedule of activities (see Section 1.3, Table 1).

Blood pressure and pulse measurements will be assessed {while the participant is in a seated position) with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of one pulse and three blood pressure measurements (three consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the three blood pressure readings will be recorded on the eCRF.

See Table 6 for details on the measurements of vital signs during administration of study treatment.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3, Table 1) using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS interval, QT interval, and QTcF interval.

All ECG recordings must be performed through use of a standard high-quality, high-fidelity digital electrocardiograph machine. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site. Digital recordings will be stored at the study site. The following should be recorded on the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QTcF based on machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted at the investigator's discretion. If a PK sample is not scheduled for that

timepoint, a PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Appendix 6. The investigator should also evaluate the participant for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

Transthoracic Echocardiogram or MUGA

TTE or MUGA scan will be performed at screening as specified in the schedule of activities (see Section 1.3, Table 1) if no scan is available from within 6 months prior to randomization. Scans may be repeated at the investigator's discretion if there are signs or symptoms of cardiotoxicity.

8.2.4 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3, Table 1) for the timing and frequency. Clinical laboratory tests conducted by a central laboratory must be conducted in accordance with the laboratory manual.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study on the Adverse Event eCRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3, Table 1, and will be conducted as outlined in Section 8.3.5.

8.2.6 Clinical Outcome Assessments

PRO questionnaires will be completed to assess the treatment effects of tobemstomig plus platinum-based chemotherapy versus pembrolizumab plus platinum-based

chemotherapy. In addition, PRO questionnaires will enable the capture of each participant's direct experience with tobemstomig in combination with platinum-based chemotherapy.

PRO data will be collected through use of the following questionnaires: selected items from the NCI PRO-CTCAE and the EORTC IL46.

The order of administration for PRO questionnaires is specified in the schedule of activities (see Section 1.3, Table 1) and are presented in Appendix 7.

[redacted] *PRO questionnaires will no longer be required.*

8.2.6.1 PRO-CTCAE

The NCI PRO-CTCAE is a validated item bank that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015). The NCI PRO-CTCAE comprises 124 questions that are rated either dichotomously (for determination of presence vs. absence) or on a 5-point Likert scale (for determination of frequency of occurrence, severity, and interference with daily function). Treatment toxicities can occur with observable signs (e.g., vomiting) or non-observable symptoms (e.g., nausea). The standard NCI PRO-CTCAE recall period is the previous 7 days.

A subset of eight signs and symptoms deemed most applicable to the current study treatments have been selected for this study (see Section A7–1.2). The signs and symptoms have been selected on the basis of the known side effects of the marketed drugs included in the standard of care, namely pembrolizumab and platinum-based chemotherapy.

8.2.6.2 EORTC Item Library 46

The EORTC IL46 is a validated single-item questionnaire assessing the overall impact of side effects (see Section A7–1.3). The standard EORTC IL46 recall period is during the previous week.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event are presented in Sections A3–1 and A3–2, respectively.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are

considered related to the study treatment or study procedures, or caused the participant to discontinue study treatment (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported (see Section A3–3.4). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until the end of the adverse event reporting period, 90 days after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3, Table 1) and as noted below.

Adverse events will be reported until 30 days after the final dose of study treatment or initiation of new systemic anti-cancer therapy, whichever occurs first. Serious adverse events will be reported until 90 days after the final dose of study treatment or initiation of new systemic anti-cancer therapy, whichever occurs first.

Adverse events of special interest will be reported until 90 days after the final dose of study treatment regardless of the initiation of new systemic anti-cancer therapy.

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Additional information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements *for expedited* safety reporting to *regulatory authorities (which includes the use of applicable systems, such as EudraVigilance),* IRBs/ECs, and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed in the following table.

Drug	Document
Tobemstomig	Tobemstomig Investigator's Brochure
Pembrolizumab	Pembrolizumab E.U. Summary of Product Characteristics
Pemetrexed	Pemetrexed E.U. Summary of Product Characteristics
Carboplatin	Carboplatin *U.K.* Summary of Product Characteristics
Paclitaxel	Paclitaxel *U.K.* Summary of Product Characteristics

EU = European Union; *U.K. = United Kingdom.*

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the respective Investigator's Brochure and Summary of Product Characteristics and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or 4 months after the final dose of tobemstomig, 4 months after the final dose of pembrolizumab, and 6 months after the final dose of platinum-based chemotherapy.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 4 months after the final dose of tobemstomig, 4 months after the final dose of pembrolizumab, *3 months after the final dose of pemetrexed,* and 6 months after the final dose of paclitaxel and carboplatin.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section A5–1.

All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Section A5–2. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Section A3–7.8.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.7)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 6.

8.3.9 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, access to Medical Monitors is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

In the previous version of the protocol, blood samples between approximately 1 and 2 mL each *were* collected for measurement of serum concentrations of tobemstomig and plasma concentrations of carboplatin (measured as total platin), paclitaxel, and pemetrexed. *From the current version of the protocol, to reduce the burden on the patients,* [redacted] *This is* specified in the schedule of activities (see Section 1.3).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of tobemstomig. Serum samples collected for analysis of tobemstomig concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these samples unless consent for this was included in an Informed Consent Form. Participant confidentiality will be maintained.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS

Refer to Sections 8.7 and 8.10.1 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

[redacted] *samples for exploratory biomarker assessments will no longer be collected. Samples collected under previous versions of the protocol may be used for exploratory biomarker assessments as detailed below.*

The following biomarker samples *were* collected *under previous versions of the protocol*, as applicable, from participants at all sites:

- Blood, plasma, serum and PBMC samples for exploratory research on biomarkers, including biomarker assay development
- Archival or newly collected tissue sample obtained at screening for EGFR or ALK mutational status assessment (if required), retrospective assessment of PD-L1 and LAG3 expression levels and for exploratory research on biomarkers, including biomarker assay development.

  A representative FFPE tumor specimen in a paraffin block (preferred) or preferably 15 slides (with an absolute minimum of 12 slides) containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment.

  Tumor tissue should be of good quality based on total and viable tumor content (i.e., a minimum number of 100 viable TCs with preserved cellular context and tissue architecture). Acceptable samples include samples from resections, core-needle biopsies for deep tumor tissue (with a minimum of three cores for freshly collected biopsies) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions, or EBUS core-needle biopsy.

EBUS-transbronchial needle aspiration is acceptable (particularly if a larger gauge needle is used), provided tissue is of good quality as described above (i.e., a minimum number of 100 viable TCs with preserved cellular context and tissue architecture). For EBUS-needle aspirations, an 18-gauge or larger needle is recommended.

Fine-needle aspirations that do not preserve tissue architecture and yield cell suspension and/or cell smears, brushings, cell pellets from pleural effusions, and lavage samples are not acceptable. Tumor tissue from bone metastases is not evaluable for tumor PD-L1 expression by IHC and is therefore not acceptable.

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if an individual's archival tissue test results do not meet eligibility criteria.

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Sections 8.10.1 and 8.10.2.

Exploratory biomarker research may include, but will not be limited to, analysis of circulating tumor DNA, genes or gene signatures associated with tumor immunobiology, lymphocytes, LAG3 and others, cytokines associated with T-cell activation, etc. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling.

Genomic research with a focus on somatic variants may be conducted by comparing DNA extracted from blood or PBMCs with DNA extracted from tissue to distinguish somatic variants from germline variants. Genomic profiling may include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, with a focus on somatic variants. WGS or WES of blood samples with a focus on germline variants may also be conducted, but only at participating sites (see Section 8.10.1).

Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.10.3), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the following exceptions:

For enrolled participants, remaining archival tissue blocks will be returned to the site upon request or no later than completion of the final Clinical Study Report, whichever occurs first. For individuals who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Antibodies to tobemstomig will be evaluated in serum samples collected from participants according to the [redacted] respectively). These samples will be tested by the Sponsor or the Sponsor's designee.

Serum samples will be screened for antibodies binding to tobemstomig and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to tobemstomig and/or to further characterize the immunogenicity of tobemstomig.

The detection and characterization of antibodies to tobemstomig will be performed through use of a validated assay method by or under the supervision of the Sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment. Samples may be stored for a maximum of 5 years (or according to local regulations) after the final Clinical Study Report has been completed at a facility selected by the Sponsor to enable further analysis of immune responses to tobemstomig.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economic and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.10.1 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing with a Focus on Germline Variants (Participants at Participating Sites)

At participating sites, blood samples *that were* collected for DNA extraction *under previous versions of this protocol may be used* to enable WGS or WES to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research *may* include exploration of germline variants. Samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 8.10.1) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or participants.

If permitted by local law, a participant may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a participant wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file but will not provide any interpretation of the data. The investigator should not include the data file in the participant's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section A1–10).

8.10.2 Tumor Biopsies (Participants Providing Separate Consent)

[redacted] *optional tumor biopsies will no longer be collected.*

Samples collected under previous versions of this protocol may be used for exploratory biomarker research as described in Section 8.7. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. Refer to Section 8.7 for information on duration of sample storage and availability of data from biomarker analyses.

8.10.3 Samples for Research Biosample Repository (Participants Providing Separate Consent at Participating Sites)

8.10.3.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR *were* collected *under previous versions of this protocol* from participants who *gave* specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.10.3.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.10.3) will not be applicable at that site.

8.10.3.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to tobemstomig, diseases, or drug safety:

- Blood, plasma, serum, and PBMC samples collected *under previous versions* of *this protocol*

- Leftover blood, serum, plasma, peripheral blood mononuclear cells, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides).

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual. RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.10.3.4 Data Protection, Use, and Sharing

RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Data generated from RBR samples will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients. In addition, given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants, unless required by law, with the exception of data generated from blood samples collected for WGS or WES as described below.

If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to

the investigator in the form of a raw genomic sequencing data file but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.10.3.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period.
A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.10.3.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the

site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.10.3.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The purpose of this study is hypothesis generation regarding the effect of tobemstomig in combination with platinum-based chemotherapy (Arm A) compared with pembrolizumab plus platinum-based chemotherapy (Arm B) on the basis of the primary endpoints, investigator-assessed ORR and PFS. No formal statistical hypotheses will be tested for this study.

9.1.1 Sample Size Determination

A total of approximately 180 patients is planned for this study.

[redacted]

[redacted] Table 8 and Table 9 show the CIs for several possible true underlying improvements in ORR and PFS in favor of Arm A.

Table 8 Confidence Intervals for Several Possible True Underlying ΔORR Values

	True Underlying ΔORR
[redacted]	

ORR = objective response rate.

[a] Calculated using Newcombe method.

Table 9 Confidence Intervals for Several Possible True Underlying PFS HR Values

	True Underlying PFS HR
[redacted]	

HR = hazard ratio; PFS = progression-free survival.

9.2 ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 10.

Table 10 Participant Analysis Sets

Participant Analysis Set	Description
Full analysis set	All randomized participants Participants will be included in the analyses according to the intervention to which they are randomized.
Measurable at baseline	All randomized participants with measurable disease at baseline, as determined by the investigator according to RECIST v1.1 Participants will be included in the analyses according to the intervention to which they are randomized.
Safety analysis set	All participants exposed to study intervention; participants will be analyzed according to the intervention they actually receive A participant will be included in Arm A (tobemstomig + chemotherapy) or Arm B (pembrolizumab + chemotherapy) in the safety analysis if the participant receives any amount of tobemstomig or pembrolizumab, regardless of the initial treatment assignment at randomization, respectively.

RECIST v1.1 = Response Evaluation Criteria is Solid Tumors, Version 1.1.

9.3 STATISTICAL ANALYSES

9.3.1 General Considerations

All efficacy analyses will be performed on the full analysis set, unless otherwise specified. The analysis of ORR will be performed for participants in all randomized participants with measurable disease at baseline, as determined by the investigator

according to RECIST v1.1. No formal hypothesis testing will be conducted; any treatment arm comparison and their associated p-value will be generated for descriptive purpose only.

All safety analyses will be performed on the safety-evaluable population, unless otherwise specified.

[redacted]

9.3.2 Estimation Methods for the Primary Endpoints

The primary efficacy endpoints are confirmed ORR and PFS, as assessed by the investigator according to RECIST v1.1.

The analysis population for ORR will be all randomized patients with measurable disease at baseline. The primary analysis of the primary endpoint of investigator-assessed ORR will occur once all randomized patients have been treated and followed until their post-baseline tumor assessment 12 weeks or 3 months after last patient has been randomized, whichever occurs first.

Investigator-assessed PFS will be analyzed in all patients randomized. [redacted] The primary analysis of the primary endpoint of investigator-assessed PFS will occur after approximately [redacted] have been observed.

9.3.2.1 Objective Response Rate

ORR is defined as the percentage of participants who experience a complete response or partial response on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to RECIST v1.1. Participants without post-baseline overall response assessments will be counted as non-responders.

An estimate of the difference between the ORR in the two arms will be computed along with its 95% CI using the Newcombe method. The 95% CI of the confirmed ORR will be calculated for each treatment arm using the Wilson score method. The Cochran-Mantel-Haenszel test will be used to compare the ORR between the two treatment arms, stratified according to the protocol-defined stratification factors.

9.3.2.2 Progression-Free Survival

PFS is defined as the time from randomization to the date of first documented disease progression or death, whichever occurs first. Disease progression for PFS analysis will be determined on the basis of investigator assessment using RECIST v1.1. Data from participants who have not experienced disease progression or who have not died at the time of analysis will be censored at the time of the last tumor assessment. Data from participants with no post-baseline tumor assessment will be censored at the date of randomization.

[redacted] be used to estimate the PFS curve and median PFS for each treatment arm. [redacted] will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982).

9.3.3 Estimation Methods for the Secondary Endpoints

9.3.3.1 Overall Survival

OS is defined as the time from randomization to death from any cause. Data for patients who are alive at the time of the data cut-off will be censored at the last date they were known to be alive. Data from participants without post-baseline information will be censored at the date of randomization.

[redacted] will be used to estimate the OS curve and median OS for each treatment arm. [redacted] will be used to construct the 95% CI for the median OS for each treatment arm (Brookmeyer and Crowley 1982). [redacted]

9.3.3.2 Duration of Response

DOR is defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first. Data from participants who have not progressed and who have not died at the time of analysis will be censored at the time of the last tumor assessment date. The analysis of DOR will include only patients who achieve an objective response to study treatment. DOR curve and median DOR for each treatment arm will be estimated according to the [redacted] will be used to construct the 95% CI for the median DOR for each treatment arm (Brookmeyer and Crowley 1982).

9.3.3.3 Investigator-Assessed PFS and OS in Selected PD-L1 Expression Subgroups

Similar analysis methods to those described for the PFS and OS analyses will be performed for participants with PD-L1 expression, [redacted]

9.3.3.4 Patient-Reported Outcomes

The change from baseline in PRO assessment of lung cancer symptoms, physical functioning, role functioning, and global health status/quality of life (GHS/QoL) as assessed through the use of the EORTC IL85, IL132, IL188, and IL17 will be analyzed for all randomized participants.

Compliance rates will be summarized by listing the number and proportion of participants who complete the PRO questionnaires at each timepoint by treatment arm.

9.3.3.5 Safety Analyses

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs.

Study treatment exposure (such as treatment duration, total dose received) will be summarized using descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms. Adverse event severity will be graded according to NCI CTCAE v5.0, with the exception of CRS event severity, which will be assessed by the investigator according to the ASTCT Consensus Grading Scale (Lee et al. 2019). All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory and vital sign will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs will be summarized.

9.3.3.6 Pharmacokinetic Analyses

Individual and mean serum *tobemstomig* concentration versus time data will be tabulated and plotted. The serum pharmacokinetics of *tobemstomig* will be summarized by estimating total exposure (AUC), maximum concentration, total clearance, volume of distribution at steady state, and terminal drug-elimination half-life (as appropriate for data collected). Estimates for these parameters will be tabulated and summarized (mean,

standard deviation, coefficient of variation, median, and range). Inter-participant variability and drug accumulation will be evaluated.

Additional PK analyses will be conducted as appropriate.

9.3.3.7 Immunogenicity Analyses

The number and proportion of ADA positive participants and ADA negative participants at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, participants are considered to be ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60-titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Participants are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60-titer unit greater than the titer of the baseline sample (treatment unaffected).

9.3.4 Exploratory Analyses

9.3.4.1 Subgroup Analysis

To assess the consistency of the study results in subgroups defined according to demographics (e.g., age, sex) and baseline disease characteristics (e.g., NSCLC histology, ECOG Performance Status), the primary efficacy endpoints in such subgroups will be examined. Summaries will be produced separately for each level of the categorical variables for comparison between treatment arms.

9.3.4.2 Patient-Reported Outcomes

The number and proportion of participants in each category of symptomatic treatment toxicities as assessed through use of selected items from the NCI PRO-CTCAE will be summarized by visit.

The number and proportion of participants in each category reporting they are troubled by treatment symptoms, as assessed through the single-item EORTC IL46 will be summarized by visit.

9.3.4.3 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.3.4.4 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics (including age, sex, race/ethnicity) will be summarized by treatment arm. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

[redacted]

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.5).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant’s legally authorized representative.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 70 sites globally will participate to enroll approximately 180 participants. Enrollment will occur through an interactive voice or web-based response system.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker, and pharmacokinetic analyses), as indicated in Section 8.2.4 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An *Internal* Monitoring Committee *was used* to monitor and evaluate participant safety throughout the study, [redacted].

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data, which may include imaging data and data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically

(e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered on the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered on the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory/central laboratory/local or central laboratory,

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count with differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes), RBC count, hemoglobin, hematocrit, platelet count, and differential count • Chemistry panel (serum): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, magnesium, potassium, chloride, calcium, phosphate, glucose, BUN or urea, creatinine, total protein, albumin, total bilirubin, ALP, ALT, AST, and lactate dehydrogenase • Coagulation: INR and aPTT • Cardiac enzymes: troponin T or troponin I • Thyroid function testing: thyroid-stimulating hormone, free T3 (or total T3 for sites where free T3 is not performed), and free T4 • HIV serology: HIV-1 antibody, HIV-1/2 antibody, and HIV-2 antibody • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test Individuals with a positive quantitative HBV DNA at screening (must be $<$500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests as outlined in the schedule of activities (see Section 1.3). • HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test • Pregnancy test: All female participants of childbearing potential will have a serum pregnancy test performed at screening within 14 days prior to initiation of study treatment. Urine or serum pregnancy tests will be performed $\leq$96 hours before Day 1 of every cycle and at the study treatment discontinuation visit. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood). If blood or protein is abnormal, microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) will be performed If there is a clinically significant positive result (confirmed by a repeat positive sample), urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded, and there is no need to perform microscopy and culture.

ADA = anti-drug antibody; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic.

Investigators must document their review of each laboratory safety report.

[redacted]

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

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a pre-existing disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- *Medically significant:*

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], or the ASTCT CRS Consensus Grade Scale; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND/OR SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) grading scale, with the exception of CRS events. The severity of CRS will be determined according to the American Society of Transplantation and Cellular Therapy (ASTCT) Consensus Grading Scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE or ASTCT.

Table A3-1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE or ASTCT CRS Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

ASTCT = American Society of Transplantation and Cellular Therapy; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

The ASTCT CRS Consensus Grading Scale (see Table A3-2) (Lee et al. 2019) should be used when reporting severity of CRS events (see Appendix 6 for details on CRS reporting).

Table A3-2 ASTCT CRS Consensus Grading Scale

Grade	Symptom(s)
1	• Fever [a], with or without constitutional symptoms • No hypotension • No hypoxia
2	• Fever [a] combined with at least one of the following: – Hypotension not requiring vasopressors – Hypoxia requiring low flow oxygen [b] by nasal cannula or blow-by
3	• Fever [a] combined with at least one of the following: – Hypotension requiring one vasopressor, with or without vasopressin – Hypoxia requiring high flow oxygen [b] by nasal cannula, face mask, non-rebreather mask, or Venturi mask
4	• Fever [a] combined with at least one of the following: – Hypotension requiring multiple vasopressors (excluding vasopressin) – Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)
5	• Death due to CRS for which the cause is not the principal factor leading to this outcome

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome.

[a] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive antipyretic, anticytokine, or corticosteroid therapy, fever is no longer required when determining CRS severity (grade). In this case, the CRS grade is driven by the presence of hypotension and/or hypoxia.

[b] Low flow is defined as oxygen delivered at ≤ 6 mL/min, and high flow is defined as > 6 L/min.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

For participants receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately

(i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information

on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/ Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 90 days after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined *as* 90 days after the final dose of study treatment), if the event is believed to be related to prior exposure to study treatment. *These events* should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF.
Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 INFUSION-RELATED REACTIONS

Adverse events that occur during or after study drug administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., infusion-related reaction [IRR]) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as “systemic reaction.” Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a participant experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

A3–7.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

For adverse events other than infusion-related reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.3 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event

eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.5 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.6 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.7 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ ULN) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.2)

and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.8 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1) that are attributed by the investigator solely to progression of non–small cell lung cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). An Internal Monitoring Committee *monitored* the frequency of deaths from all causes [redacted]. *Deaths will continue to be monitored at regular intervals by the study management team.*

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.9 PRE-EXISTING MEDICAL CONDITIONS

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.10 LACK OF EFFICACY OR WORSENING OF NON–SMALL CELL LUNG CANCER

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of non–small cell lung cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of non–small cell lung cancer"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on Response Evaluation Criteria in Solid Tumors, Version 1.1 (see Appendix 10). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A3–7.11 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study)
- Hospitalization for a pre-existing condition, provided that both of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition.
  - The participant has not experienced an adverse event.
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.12 CASES OF ACCIDENTAL OVERDOSE AND MEDICATION ERROR

Accidental overdose and medication error are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations and adverse events associated with special situations are to be reported separately on the Adverse Event eCRF, as outlined in the sections below.

A3–7.12.1 Reporting Special Situations

All special situations associated with tobemstomig, pembrolizumab, pemetrexed, carboplatin, and paclitaxel regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: tobemstomig, pembrolizumab, pemetrexed, carboplatin, and paclitaxel administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

A3–7.12.2 Reporting Adverse Events Associated with Special Situations

Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the

Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). For tobemstomig, pembrolizumab, pemetrexed, carboplatin, and paclitaxel adverse events associated with special situations should be recorded as described below for each situation:

- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose (special situation) and one entry to report the adverse event (headache). The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

A3–7.13 CASES OF MEDICATION ERROR

A medication error is defined as an accidental deviation in the administration of a drug (e.g., wrong drug dose administered, sham procedure performed in participant assigned to active drug, drug administered in wrong location, sham procedure performed incorrectly, expired drug administered). In some cases, a medication error may be intercepted prior to administration of the drug.

Medication errors are not in themselves adverse events but may result in adverse events. The unmasked treating physician will record each adverse event associated with a medication error on a paper adverse event reporting worksheet and will indicate that a "medication error" has occurred. The unmasked treating physician will not indicate the type of medication error or provide any other information that could reveal the participant's treatment assignment. The masked assessor physician will then assess the causality of the adverse event and enter this information on the worksheet.
A masked site team member will record each adverse event on the Adverse Event eCRF by entering the adverse event term and checking the "Medication error" box. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

The unmasked treating physician will record information about each medication error, regardless of whether it resulted in an adverse event, on a two-page paper study treatment administration worksheet. The unmasked treating physician will provide detailed information on the first page of the worksheet and will indicate on the second page that a "medication error" has occurred. The second page of the worksheet will not indicate the type of medication error or provide any other information that could reveal

the participant's treatment assignment. The first page will be archived with study records that are accessible only to unmasked personnel. The second page will be forwarded to a masked site team member, who will record the medication error on the Adverse Event eCRF by entering "Medication error" as the event term and checking the "Medication error" box.

As an example, a medication error that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report a medication error and one entry to report the headache. The "Medication error" boxes would need to be checked for both entries.

A3–7.14 PATIENT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) or other patient-reported outcome (PRO) data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile participant reports of treatment-related symptoms (through the use of the PRO-CTCAE) with investigator reports of adverse events. Sites are not expected to review the PRO-CTCAE or other PRO data for adverse events.

A3–7.15 SAFETY BIOMARKER DATA

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

REFERENCES

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

Appendix 4
Safety Plan: Management of Identified and Potential Risks

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A4–1 RISKS ASSOCIATED WITH TOBEMSTOMIG

Infusion-related reactions are *an* identified *risk* with tobemstomig*, and* [redacted]. . The potential risks associated with tobemstomig are comparable to the potential risks of therapeutic antibodies generally and the potential risks generally associated with programmed death–ligand 1 (PD-1) and lymphocyte activation gene 3 (LAG3) receptor–targeting agents and *include* immunogenicity and immune-mediated adverse events*. For more details relating to the risks associated with tobemstomig, refer to the Tobemstomig Investigator's Brochure*.

A4–2 RISKS ASSOCIATED WITH PEMBROLIZUMAB

Pembrolizumab has been associated with immune-mediated risks, such as pneumonitis, colitis, hepatitis, nephritis, endocrinopathies (adrenal insufficiency, hypophysitis, Type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism), skin adverse reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), and other immune-mediated adverse reactions (uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, hemolytic anemia, sarcoidosis, encephalitis, myelitis, cholangitis sclerosing, gastritis, and non-infective cystitis). Infusion-related reactions are identified risks with pembrolizumab. Pembrolizumab in combination with chemotherapy should be used with caution in participants who are ≥75 years old after careful consideration of the potential benefits and risks on a case-by-case basis.

For more details regarding the safety profile of pembrolizumab, refer to the pembrolizumab prescribing information.

A4–3 RISKS ASSOCIATED WITH PEMETREXED

Pemetrexed is known to cause gastrointestinal toxicities (nausea, vomiting, diarrhea, or constipation), renal toxicities, neuropathy, myelosuppression, infection, fatigue, stomatitis, alopecia, and rash.

For more details regarding the safety profile of pemetrexed, refer to the prescribing information for pemetrexed.

A4–4 RISKS ASSOCIATED WITH CARBOPLATIN

Carboplatin is known to cause bone marrow suppression, including myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic. Participants will be monitored for carboplatin-related adverse events.

For more details regarding the safety profile of carboplatin, refer to the carboplatin prescribing information.

A4–5 RISKS ASSOCIATED WITH PACLITAXEL

Paclitaxel is known to cause bone marrow suppression (e.g., myelosuppression, anemia and thrombocytopenia), gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), hepatotoxicity, peripheral neuropathy, hypersensitivity reactions, arthralgia or myalgia, injection site reactions, alopecia, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, and other ECG abnormalities. Patients will be monitored for paclitaxel-related adverse events. For more details regarding the safety profile of paclitaxel, refer to the paclitaxel prescribing information.

A4–6 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A4–6.1 DOSE MODIFICATIONS FOR TOBEMSTOMIG AND PEMBROLIZUMAB

There will be no dose modifications, including dose reductions for tobemstomig and pembrolizumab in this study.

A4–6.2 DOSE MODIFICATIONS FOR CHEMOTHERAPY

Dose modifications for pemetrexed, paclitaxel, and carboplatin are permitted for toxicity according to the prescribing information and local standard of care.

Dose modification guidelines are provided below. Once reduced, the dose cannot be increased back to 100%.

Treatment with pemetrexed and carboplatin should be discontinued if a patient experiences any hematologic or non-hematologic Grade 3 or Grade 4 toxicity after two dose reductions or treatment is delayed for more than 63 days due to toxicities.

A4–6.2.1 Hematologic Toxicity

At the start of each cycle, the ANC should be $\geq$1500/μL and the platelet count should be $\geq$100,000/μL. Treatment may be delayed for up to 63 days to allow sufficient time for recovery. Growth factors may be used in accordance with American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) guidelines (Smith et al. 2015; NCCN 2019). Upon recovery, dose adjustments at the start of a subsequent cycle will be made on the basis of the lowest platelet and neutrophil values from the previous cycle (see Table A4-1).

Table A4-1 Chemotherapy Dose Modifications for Hematologic Toxicities

Toxicity [a]	Dose
ANC $<$ 500/μL and platelets $\geq$ 50,000/μL	75% of previous dose
Platelets $<$ 25,000/μL, regardless of ANC	75% of previous dose
Platelets $<$ 50,000/μL with Grade $\geq$ 2 bleeding, regardless of ANC	50% of previous dose
ANC $<$ 1000/μL plus fever of $\geq$ 38.5°C	75% of previous dose

[a] Nadir at prior cycle.

In the event that dose adjustments are needed for both ANC and platelets, participants are to receive the lower dose.

Investigators should be vigilant and alert to early and overt signs of myelosuppression, infection, or febrile neutropenia so that these complications can be promptly and appropriately managed. Participants should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

If chemotherapy is withheld because of hematologic toxicity, complete blood counts (including differential WBC) should be obtained weekly until the counts reach the lower limits for treatment as outlined. Treatment can then be resumed.

No dose reductions are recommended for anemia. Participants should be supported per the investigator's institution's guidelines.

A4–6.2.2 Non-Hematologic Toxicity

For a non-hematologic toxicity (see Table A4-2), treatment should be delayed for up to 63 days until resolution to less than or equal to the participant's baseline value or Grade 1 or better if the participant did not have that toxicity at baseline).
Dose reductions at the start of the subsequent cycle should be made on the basis of non-hematologic toxicities from the dose administered in the preceding cycle.
The recommended dose modifications for non-hematologic toxicities are presented in Table A4-2.

Table A4-2 Dose Modifications for Treatment Discontinuation for Non-Hematologic Toxicities

Toxicity		Adjusted Dose as Percentage of Previous Dose [a]
Diarrhea	Grade 3 or 4 [b]	75%
Nausea or vomiting	Grade 3 or 4 [c]	75%
Neurotoxicity	Grade 2	75%
	Grade 3 or 4	50% or permanent discontinuation
Transaminase elevation	Grade 3	75%
	Grade 4	Discontinue.
Other	Grade 3 or 4	75%

[a] If deemed appropriate by the investigator, adjust carboplatin dose to the specified percentage of the previous area under the concentration–time curve.

[b] Grade 3 or 4 diarrhea that occurs on adequate anti-diarrhea medication or any grade of diarrhea requiring hospitalization.

[c] Despite the use of anti-emetic therapies.

Diarrhea should be controlled with adequate antidiarrheal medication. Nausea and/or vomiting may be controlled with adequate anti-emetic medications. For Grade 3 or 4 neurotoxicity chemotherapy should be resumed at 50% of the previous dose upon improvement or discontinued immediately (based on the investigator's clinical judgment).

A4–6.3 TREATMENT INTERRUPTION FOR TOBEMSTOMIG AND PEMBROLIZUMAB

Before permanently discontinuing tobemstomig or pembrolizumab (regardless of whether initiated by the participant, the investigator, or the Sponsor), an interruption should be considered. Participants who have temporarily interrupted tobemstomig or pembrolizumab should be considered to restart treatment as soon as medically justified in the opinion of the investigator.

Tobemstomig or pembrolizumab may be temporarily suspended for up to 12 weeks to allow for resolution of toxicity to NCI CTCAE Grade ≤ 2 for hematological toxicities or Grade 1 or better for non-hematological toxicities (with the exception of a toxicity considered by the investigator to be non-study treatment-related). If tobemstomig/pembrolizumab is withheld for ≥ 12 weeks, the participant will be discontinued from tobemstomig or pembrolizumab.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed, and the acceptable length of interruption should be discussed between the investigator and the Medical Monitor. Minor elective surgery will generally be permitted

during the study with resumption of tobemstomig or pembrolizumab as soon as possible post-procedure, assuming normal recovery. This can be done to avoid the discontinuation of participants who could potentially benefit from study treatment.

It should be noted that infusions and cycles not occurring at the anticipated schedule, are considered as delayed, not missed.

If a participant has a complete response or achieves maximum clinical benefit as determined by the investigator and the Sponsor after an integrated assessment of radiographic data, biopsy results (if available), and clinical status. Tobemstomig and pembrolizumab may be paused at the discretion of the investigator after discussion with the Medical Monitor. While treatment with tobemstomig or pembrolizumab is paused, assessments per the schedule of activities (see Section 1.3, Table 1) will be suspended, except for tumor assessments. The length of the treatment pause is to be included in the calculation of the maximum duration of treatment (*24* months from Day 1 of Cycle 1 to the discontinuation visit) as per Section 4.5.

A4–6.4 MANAGEMENT GUIDELINES

A4–6.4.1 Management Guidelines for Adverse Events Associated with Tobemstomig and Pembrolizumab

See Appendix 6 for details on the management of tobemstomig and pembrolizumab-associated adverse events. See Appendix 9 for precautions for anaphylaxis.

A4–6.4.2 Chemotherapy Dose Modifications, Treatment Delays, or Treatment Discontinuation and Management of Specific Adverse Events

See Appendix 6 for details on chemotherapy dose modifications, treatment delays, or treatment discontinuation and management of specific adverse events.

A4–6.4.3 Potential Overlapping Toxicities

The risk of overlapping toxicities between tobemstomig or pembrolizumab in combination with paclitaxel or pemetrexed and carboplatin is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin, and gastrointestinal toxicity) may be ambiguous when the agents are administered together. It is theoretically possible that allergic or inflammatory adverse events associated with pemetrexed, paclitaxel, and carboplatin (e.g., dermatitis, infusion-associated symptoms) could be exacerbated by the immunostimulatory activity of tobemstomig and pembrolizumab.

Toxicities should initially be managed according to the recommendations in Appendix 6 with dose holds and modifications (if applicable) applied to the component of the study drug judged to be the primary cause. If, in the opinion of the investigator, tobemstomig or pembrolizumab is a potential inciting factor, the dose of tobemstomig or pembrolizumab may be held for a maximum of 12 weeks (or four cycles) beyond the last infusion (see Appendix 6). Tobemstomig and pembrolizumab can be resumed after being withheld for > 12 weeks if the participant is likely to derive clinical benefit. The decision to rechallenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. Prompt symptomatic management is appropriate for mild immune-mediated adverse events. In severe cases, immune-mediated toxicities may be acutely managed with systemic corticosteroids or tumor necrosis factor inhibitors. The Medical Monitor is available to advise as needed.

REFERENCES

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Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2015;33:3199–212.

Appendix 5
Collection of Pregnancy Information

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A5–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 4 months after the final dose of tobemstomig, 4 months after the final dose of pembrolizumab, and 6 months after the final dose of platinum-based chemotherapy. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A5–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 4 months after the final dose of tobemstomig, 4 months after the final dose of pembrolizumab*, 3 months after the final dose of pemetrexed,* and 6 months after the final dose of paclitaxel and carboplatin. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would

need to sign an Authorization for Use and Sharing of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A5–3 ABORTIONS

A spontaneous abortion in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A5–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment

should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 6
Risks Associated with Tobemstomig and Pembrolizumab and Guidelines for Management of Adverse Events Associated with Tobemstomig or Pembrolizumab

Toxicities associated or possibly associated with tobemstomig and pembrolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of tobemstomig or pembrolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections:

- Patients and family caregivers should receive timely and up to date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment-related.
- In general, tobemstomig and pembrolizumab should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider holding tobemstomig and pembrolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- Hold tobemstomig and pembrolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before tobemstomig and pembrolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of a tobemstomig and pembrolizumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.

The investigator should consider the benefit–risk balance a given participant may be experiencing prior to further administration of tobemstomig or pembrolizumab.

Resumption of tobemstomig or pembrolizumab may be considered in participants deriving benefit and have fully recovered from the immune-mediated event.
The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

MANAGEMENT GUIDELINES

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. COVID-19 evaluation should be performed per institutional guidelines where relevant. Management guidelines for pulmonary events are provided in Table A6-1.

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue tobemstomig or pembrolizumab monitor closely. • Re-evaluate on serial imaging. • Consider participant referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding tobemstomig or pembrolizumab.
Pulmonary event, Grade 2	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Refer participant to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c] [d] • For recurrent events or events with no improvement after 48−72 hours of corticosteroids, treat as a Grade 3 or 4 event.

BAL = bronchoscopic alveolar lavage.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] In case of pneumonitis, tobemstomig or pembrolizumab should not be resumed after permanent discontinuation.

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

Event	Management
Pulmonary event, Grade 3 or 4	• Permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c] • Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. • Bronchoscopy or BAL with or without transbronchial biopsy is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

[d] In case of pneumonitis, tobemstomig or pembrolizumab should not be resumed after permanent discontinuation.

HEPATIC EVENTS

Participants eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A6-2.

Participants with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug(s).

For participants with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table A6-2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue tobemstomig or pembrolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c]

LFTs = liver function test.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4 or liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	• Permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c] • Consider participant referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFTs = liver function test.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A6-3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table A6-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue tobemstomig or pembrolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. • Participant referral to GI specialist is recommended. • For recurrent events or events that persist $>$ 5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Refer participant to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c]

Table A6-3 Management Guidelines for Gastrointestinal events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c] • Refer participant to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A6-4.

Participants with unexplained symptoms, such as headache, fatigue, myalgias, impotence, constipation, or mental status changes, should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The participant should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table A6-4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue tobemstomig or pembrolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• Consider withholding tobemstomig or pembrolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume tobemstomig or pembrolizumab when symptoms are controlled and thyroid function is improving.
Grade 3 and 4 hypothyroidism	• Withhold tobemstomig or pembrolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Refer to an endocrinologist. • Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). • Resume tobemstomig or pembrolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue tobemstomig or pembrolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • Consider patient referral to endocrinologist.
Grade 2 hyperthyroidism	• Consider withholding tobemstomig or pembrolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume tobemstomig or pembrolizumab when symptoms are controlled and thyroid function is improving.
Grade 3 and 4 hyperthyroidism	• Withhold tobemstomig or pembrolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • Refer to endocrinologist. • Resume tobemstomig or pembrolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grades 2–4	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Refer participant to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and participant is stable on replacement therapy, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hyperglycemia, Grade 1 or 2	• Continue tobemstomig or pembrolizumab. • Investigate for diabetes. If participant has Type 1 diabetes, treat as a Grade 3 event. If participant does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold tobemstomig or pembrolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume tobemstomig or pembrolizumab when symptoms resolve, and glucose levels are stable.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (panhypopituitarism-), Grade 2 or 3	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (panhypopituitarism-), Grade 4	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c] • Refer participant to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A6-5.

Table A6-5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue tobemstomig or pembrolizumab. • Participant referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Participant referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c] • Refer participant to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table A6-6.

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis should be suspected in any participant presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on pericardial disorders below) and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a participant who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of pre-existing cardiac conditions, or progression of malignancy.

All participants with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Participants with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-6.

IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post-myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as

appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-6.

Table A6-6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2–4 Immune-mediated pericardial disorders, Grades 2–4	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [a] • Refer participant to cardiologist. • Initiate treatment as per institutional guidelines and consider anti-arrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

INFUSION-RELATED REACTIONS

Administration of therapeutic antibodies may cause infusion-related reactions (IRRs), characterized by symptoms, such as fever, chills, dizziness, hypertension, hypotension, dyspnea, restlessness, sweating, flushing, skin rash, tachycardia, tachypnea, headache, tumor pain, nausea, and/or vomiting. Respiratory and cardiac symptoms such as, bronchospasm, larynx, and throat irritation, wheezing, laryngeal edema, and atrial fibrillation may also occur. Such reactions typically occur during or shortly after an infusion or within 24 hours after study treatment infusion, predominantly at the first infusion. The incidence and severity typically decrease with subsequent infusions.

Participants may also develop IgE-mediated hypersensitivity reactions. IRRs may be indistinguishable from an anaphylactic reaction; however, in case of IgE-mediated hypersensitivity, symptoms typically occur after previous exposure and very rarely with the first infusion. In case of confirmed IgE-mediated hypersensitivity reaction, treatment should be permanently discontinued.

No premedication is indicated for the administration of Cycle 1 of pembrolizumab and tobemstomig. However, participants who experience a Grade $\geq$2 IRR with tobemstomig or pembrolizumab should receive premedication for subsequent infusions (see Section 6.8.1) with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions. In case of Grade 4 IRR related to tobemstomig or pembrolizumab, the participant should be permanently discontinued from the study treatment. If an IRR occurs during the infusion of tobemstomig or pembrolizumab. Metamizole (dipyrone) is prohibited in treating pembrolizumab-associated IRRs because of its potential for causing agranulocytosis.

Guidelines for medical management of IRRs during Cycle 1 are presented in Table A6-7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table A6-7 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grades 1 and 2	• Reduce infusion rate to ≤ 50% of the rate being given at the time of event onset or interrupt infusion. • Give supportive treatment. • Upon symptom resolution, the infusion may be resume (if interrupted) at 50% of the starting rate. The infusion must remain at the lower rate resulting in symptom resolution for the remainder of the infusion. • For Grade 2 IRRs, subsequent cycles of tobemstomig or pembrolizumab should be administered with premedication, including acetaminophen or paracetamol and an antihistamine, such as diphenhydramine. • For Grade 2 wheezing or urticaria, the participant must also be premedicated prior to subsequent doses as described above. • If symptoms recurs at the same or greater severity following the slower infusion rate or interruption, the infusion must be stopped immediately. No additional tobemstomig or pembrolizumab will be administered for that cycle.
IRR, Grade 3 and 4	• Discontinue infusion immediately. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). • Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [a]

IRR = infusion-related reaction.

[a] Resumption of tobemstomig and pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with tobemstomig and pembrolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator. The Medical Monitor is available to advise as needed.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin-6, interleukin-10, interleukin-2, and interferon-γ (Merad and Martin 2020). If a participant develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

CYTOKINE RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of tobemstomig or pembrolizumab. However, participants who experience CRS with tobemstomig or pembrolizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well-documented with chimeric antigen receptor T-cell therapies and bispecific T-cell–engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including tobemstomig or pembrolizumab

Guidelines for medical management of CRS are provided in Table A6-8.

Table A6-8 Management Guidelines for Cytokine Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (> 2 days) or in participants with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize participant (monitoring in the ICU is recommended), permanently discontinue tobemstomig or pembrolizumab, and contact the Medical Monitor. • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of tobemstomig or pembrolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Medical Monitor.

Table A6-8 Management Guidelines for Cytokine Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in an ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize participant until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit participant to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for participants who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) **and/or** Hypoxia requiring oxygen by positive pressure (e.g., CPAP, Bi-PAP, intubation and mechanical ventilation)	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit participant to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For participants who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize participant until complete resolution of symptoms.

Table A6-8 Management Guidelines for Cytokine Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; Bi-PAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE v5.0 = Common Terminology Criteria for Adverse Events, Version 5.0; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] The grading system for management guidelines is based on the ASTCT CRS Consensus Grading Scale (see Section A3–3.2 and Table A3-2). The ASTCT CRS Consensus Grading Scale should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine Release Syndrome eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In participants who develop CRS and then receive antipyretic, anticytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretic medications, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessment of the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table A6-9.

Table A6-9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5–2.0 × ULN:** • Continue tobemstomig or pembrolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Refer participant to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c]

GI = gastrointestinal; ULN = upper limit of normal.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-9 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Refer participant to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c] • Refer participant to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal; ULN = upper limit of normal.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

DERMATOLOGIC EVENTS

Treatment-emergent rash may be associated with tobemstomig or pembrolizumab. The majority of cases of rash reported with the use of pembrolizumab were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with pembrolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table A6-10.

Table A6-10 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue tobemstomig or pembrolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue tobemstomig or pembrolizumab. • Consider participant referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Refer participant to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c]

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-10 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold tobemstomig or pembrolizumab and for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring participant to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue tobemstomig or pembrolizumab.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

NEUROLOGIC DISORDERS

Participants may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table A6-11.

Table A6-11 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue tobemstomig or pembrolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer participant to neurologist. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c] • Refer participant to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. • Refer participant to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any participant presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All participants being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Participants with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-12.

Table A6-12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [a] • Refer participant to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

RENAL EVENTS

Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Participants with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the participant to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Participants with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-13.

Table A6-13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue tobemstomig or pembrolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset. [a] • Refer participant to renal specialist. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig, permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue tobemstomig or pembrolizumab and contact Medical Monitor. • Refer participant to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography or MRI) features and is confirmed with a muscle biopsy. Participants with possible myositis should be referred to a rheumatologist or neurologist. Participants with possible myositis should be monitored for signs of myocarditis.

Participants with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-14.

Table A6-14 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue tobemstomig or pembrolizumab. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c]

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold tobemstomig or pembrolizumab for up to 12 weeks after event onset [a] and contact the Medical Monitor. • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume tobemstomig or pembrolizumab. [b] • If event does not resolve to Grade 1 or better while withholding tobemstomig or pembrolizumab, permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

Table A6-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. [c] • Refer participant to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if participant is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Tobemstomig or pembrolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on the investigator's assessment of the benefits and risks and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before tobemstomig or pembrolizumab can be resumed.

[c] Resumption of tobemstomig or pembrolizumab may be considered in participants who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge participants with tobemstomig or pembrolizumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator. The Medical Monitor is available to advise as needed.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or is prolonged.

Participants with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A participant should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (< 9 g/dL) (< 100 g/L [< 10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L ($< 100{,}000/\mu$L)
  - ANC $< 1.0 \times 10^9$/L ($< 1000/\mu$L)
- Fasting triglycerides > 2.992 mmol/L (> 265 mg/dL) and/or fibrinogen < 1.5 g/L (< 150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (> 500 ng/mL)
- Soluble interleukin-2 receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Participants with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile participant should be classified as having MAS if the following criteria are met:

- Ferritin > 684 mg/L (> 684 ng/mL)
- At least 2 of the following:
  - Platelet count $\leq 181 \times 10^9$/L ($\leq 181{,}000/\mu$L)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (> 156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (≤ 360 mg/dL)

Participants with suspected HLH or MAS should be treated according to the guidelines in Table A6-15.

Table A6-15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue tobemstomig or pembrolizumab and contact the Medical Monitor. • Consider participant referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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Appendix 7
Clinical Outcome Assessments

TABLE OF CONTENTS

A7–1 CLINICAL OUTCOME ASSESSMENTS

Patient-reported outcome (PRO) questionnaires will be self-administered or interviewer administered (as appropriate) at the clinic or by site personnel by telephone at specified timepoints during the study (see the schedule of activities in Section 1.3, Table 1). At the clinic, questionnaires will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

PRO questionnaires, translated into the local language as appropriate, will be provided by the Sponsor in preprinted booklets to enable the appropriate questionnaires to be administered in the correct order at each specified timepoint.

PRO assessments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the questionnaires.
- Sites must administer the official version of each questionnaire, as provided by the Sponsor. Questionnaires must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the questionnaires.
- Sites should administer the questionnaires in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the questionnaires.
- Participants whose native language is not available with the questionnaires are exempted from completing all PRO assessments.

Site staff should review all completed questionnaires and should ask the participants to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the participant to complete the item or confirm that the item was intentionally left blank.

A7–1.1 EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER ITEM LIBRARIES

A7–1.1.1 Item Library 85

ENGLISH

EORTC IL85

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
1.	How much did you cough?	1	2	3	4
2.	Were you short of breath when you rested?	1	2	3	4
3.	Were you short of breath when you walked?	1	2	3	4
4.	Were you short of breath when you climbed stairs?	1	2	3	4
5.	Have you had pain in your chest?	1	2	3	4

A7–1.1.2 Item Library 132

ENGLISH

EORTC IL132

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
1. Did you need to rest?	1	2	3	4
2. Have you felt weak?	1	2	3	4
3. Were you tired?	1	2	3	4

A7–1.1.3 Item Library 188

ENGLISH

EORTC IL188

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
1. Have you had aches or pains in your bones?	1	2	3	4

A7–1.1.4 Item Library 17

ENGLISH

EORTC IL17

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

8. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

9. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

A7–1.2 SELECTED ITEMS FROM THE NATIONAL CANCER INSTITUTE PATIENT-REPORTED OUTCOMES COMMON TOXICITY CRITERIA FOR ADVERSE EVENTS

NCI PRO-CTCAE® ITEMS

Item Library Version 1.0
English
Form Created on 8 April 2022

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
1b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

2a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
2b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

3a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
3b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

4a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

5a. In the last 7 days, did you have any RASH?	
O Yes	O No

6a. In the last 7 days, did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

7a. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

8a. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
8b. In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
8c. In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

A7–1.3 ITEM LIBRARY 46

ENGLISH

EORTC IL46

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
1. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4

Appendix 8
Pre-Existing Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering tobemstomig and pembrolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty about autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

Acute disseminated encephalomyelitis	Dermatomyositis	Neuromyotonia
Addison disease	Diabetes mellitus, type 1	Opsoclonus myoclonus syndrome
Ankylosing spondylitis	Dysautonomia	Optic neuritis
Anti-phospholipid antibody syndrome	Epidermolysis bullosa acquisita	Ord thyroiditis
Aplastic anemia	Gestational pemphigoid	Pemphigus
Autoimmune hemolytic anemia	Giant cell arteritis	Pernicious anemia
Autoimmune hepatitis	Goodpasture syndrome	Polyarteritis nodosa
Autoimmune hypoparathyroidism	Granulomatosis with polyangiitis	Polyarthritis
Autoimmune hypophysitis	Graves disease	Polyglandular autoimmune syndrome
Autoimmune myocarditis	Guillain-Barré syndrome	Primary biliary cholangitis
Autoimmune oophoritis	Hashimoto disease	Psoriasis
Autoimmune orchitis	IgA nephropathy	Reiter syndrome
Autoimmune thrombocytopenic purpura	Inflammatory bowel disease	Rheumatoid arthritis
Behçet disease	Interstitial cystitis	Sarcoidosis
Bullous pemphigoid	Kawasaki disease	Scleroderma
Chronic fatigue syndrome	Lambert-Eaton myasthenia syndrome	Sjögren syndrome
Chronic inflammatory demyelinating polyneuropathy	Lupus erythematosus	Stiff-Person syndrome
Churg-Strauss syndrome	Lyme disease, chronic	Takayasu arteritis
Crohn disease	Meniere syndrome	Ulcerative colitis
	Mooren ulcer	Vitiligo
	Morphea	Vogt-Koyanagi-Harada disease
	Multiple sclerosis	
	Myasthenia gravis	

Appendix 9
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for IM (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.
7. *Collect laboratory sample of serum tryptase within 1–6 hours of the anaphylactic reaction after the patient stabilizes.*
8. *Ask the participant to return for immunogenicity sample collection at 3 weeks postdose, if appropriate.*

Appendix 10
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009; Schwartz et al. 2016), are presented below, with the addition of explanatory text as needed for clarity.

TUMOR MEASURABILITY

At baseline, tumor lesions and lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lungs, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, positron emission tomography (PET) scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and not usually more than 4 weeks prior to the beginning of treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter assessed using calipers (e.g., skin nodules). For the case of skin

lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without MRI IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (with or without MRI IV contrast) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible, and <u>if not, the patient</u> <u>should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality because the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, AND HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

<u>Assessment of Tumor Burden</u>

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that on occasion the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20×30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, given that a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but is too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but is too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

  To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce during Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining the maximal diameter measurements of each individual lesion. If the lesions have truly

coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in the short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "unequivocal progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the following criteria used to determine objective tumor response for target lesions are provided:

- Complete response (CR): disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): at least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): neither sufficient shrinkage to qualify for a CR or a PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: disappearance of all non-target lesions

  All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/non-PD: persistence of one or more non-target lesions
- PD: unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show a PR or a CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. In certain situations, as defined in Section 4.1.5, participants might be treated beyond progression. Therefore, the size of measurable new lesions will be captured in the eCRF to allow assessing the benefit of treating participants beyond progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it truly represents new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared as of the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A10-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients.

Table A10-1 Criteria for Overall Response at a Single Timepoint

Target Lesions	Non-Target Lesions	New Lesions	Timepoint Response
CR	CR	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR, non-CR/non-PD, or NE	No	PR
SD	CR, non-CR/non-PD, or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
CR	NED [b]	No	CR
PR	NED [b]	No	PR
SD	NED [b]	No	SD
NED [a]	Non-CR/non-PD	No	Non-CR/non-PD
NED [a]	CR	No	CR
NED [a]	NE	No	NE
NED [a]	NED [b]	No	NED

CR = complete response; NE = not evaluable; NED = not evaluable disease; PD = progressive disease; PR = partial response; SD = stable disease.

[a] No target lesions identified at baseline

[b] No non-target lesions identified at baseline.

MISSING ASSESSMENTS AND NOT EVALUABLE DESIGNATION

When no imaging or measurement is performed at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a

descriptor of an objective response; it is a reason for stopping study treatment. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A10-1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Fluorodeoxyglucose (FDG)-PET is **not yet validated** for use in clinical trials to determine response but may complement CT/MRI in the assessment of progression.

FDG-PET imaging to identify new lesions is described in the following table.

Baseline FDG-PET	Post-Baseline FDG-PET	Determination
Negative FDG-PET	Positive FDG-PET	New lesion (PD)
None	Positive FDG-PET corresponds to a new site of disease confirmed by CT/MRI	New lesion (PD)
None	Positive FDG-PET not confirmed as a new site of disease on CT/MRI	Additional follow-up CT/MRI scans are needed to determine if there is truly progression occurring at that site. If so, new lesion (PD) with the date of PD being the date of the initial abnormal FDG-PET scan date If not, it is not a new lesion.
None	Positive FDG-PET that corresponds to a pre-existing site of disease on CT/MRI that is not progressing on the basis of the anatomic images	Not a new lesion

CT = computed tomography; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PD = progressive disease; PET = positron emission tomography.

Note: A positive FDG-PET scan lesion indicates one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Schwartz LH., Litiére S, de Vries SE, et al. RECIST 1.1–update and clarification: from RECIST Committee. Eur J Cancer 2016;62:132–7.

Appendix 11
Eastern Cooperative Oncology Group Performance Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 12
Genetics: Use and Analysis of DNA for Mandatory Samples

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to tobemstomig, and non–small cell lung cancer and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to tobemstomig and non–small cell lung cancer. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome.

DNA samples will be analyzed for exploratory safety and efficacy analyses. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to tobemstomig or study treatments of this class to understand non–small cell lung cancer or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on tobemstomig and non–small cell lung cancer continues but no longer than 15 years after the final Clinical Study Report has been completed or other period as per local requirements.

Appendix 13
Investigational, *Authorized Auxiliary,* and *Unauthorized Auxiliary* Medicinal Product Designations (for Use in European Economic Area)

Product Name	IMP/*Ax*MP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Tobemstomig (RO7247669)	IMP (test product)	Not authorized	No
Pembrolizumab	IMP (comparator)	Authorized	Yes
Pemetrexed	IMP (other) [a]	Authorized	No [b]
Paclitaxel	IMP (other) [a]	Authorized	No [b]
Carboplatin	IMP (other) [a]	Authorized	No [b]

AxMP= auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.

[a] A secondary objective of the study is to investigate the pharmacokinetics of tobemstomig in combination with paclitaxel or pemetrexed and carboplatin.

[b] Pemetrexed, paclitaxel, and carboplatin are approved for the treatment of non–small lung cancer but are not approved in combination with tobemstomig.

Appendix 14
Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 2: (31 OCTOBER 2022)

Protocol BO44178 has been amended to address comments received from the Food and Drug Administration (FDA) along with other changes and clarifications. Changes to the protocol, along with a rationale for each change, are summarized below.

- Following an FDA request, the following was updated to minimize the number of patients exposed to the experimental arm while an approved regimen exists:
  - Randomization ratio updated from 2:1 to 1:1 (Figure 1, Section 4.1, 4.1.2).
  - Sample size has been reduced from 210 to 180. Specifically, the number of patients in each arm has been adjusted with experimental arm reduced from 140 to 90, Arm B increased from 70 to 90 (Figure 1, Sections 4.1, 4.1.2, 4.1.3, 5, 9.1.1, Appendix 1).
  - [redacted]
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol. Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites (front matter and Section 8.3.9).
- The synopsis has been simplified in preparation for the Clinical Trial Regulation (CTR) in the EU (Section 1.1).
- [redacted]
- The Independent Data Monitoring Committee has been replaced by an Internal Monitoring Committee (IMC) whose remit will include the safety run-in analysis [redacted]. Periodic reviews of safety data will be performed by an IMC, specifically to make recommendations regarding study conduct on the basis of emerging trial safety data to ensure patient safety while receiving study treatment. An IMC will be better positioned to incorporate the totality of data from Study BO44178 and other studies with RO7247669 to inform their recommendations (Figure 1, Sections 4.1.3, 4.1.8, 9.4.1).
- Epstein-Barr virus (EBV) exclusion is not relevant for this study, thus EBV testing is not required (Table 1, and Appendix 2, Table A2-1).

- The schedule of activities has been updated to correct a typographic error regarding the patient-reported outcome questionnaires. Q356 has been corrected to IL188 (Table 1).
- Optional blood sample collections for the Research Biosample Repository have been added for participants who give specific consent to participate in this optional exploratory research (Table 1, Table 2, Section 8.10.3.3).
- Transthoracic echocardiogram or multiple-gated acquisition scan has been added to schedule of activities to be performed at screening if no scan is available from within 6 months prior to initiation of study treatment, as this is an inclusion criterion (Table 1, Section 8.2.3).
- Language has been updated to clarify that *EGFR/ALK* testing at screening is not required for squamous NSCLC patients with unknown mutational status prior to enrollment as *EGFR/ALK* genomic aberrations are uncommon in patients with this histology (Table 1, Section 4.1.1, 5.2).
- Blood sample collections for pemetrexed, carboplatin and paclitaxel pharmacokinetics at Cycle 1 and Cycle 5, 6 hours post dose have been removed in order to reduce patient burden (Table 2).
- Additional detail on safety and tolerability data from previous studies was added to the benefit-risk profile (Section 2.3).
- The number of participants in Arm A and Arm B of the safety run-in evaluation have been adjusted, based on the changes to the study design (Section 4.1.3).
- Language was added to allow capturing the size of new lesions in the eCRF, in order to allow assessing the benefit of treating participants beyond progression (Section 4.1.5, Appendix 10)
- The dose rationale has been expanded to provide further explanation for the [redacted] mg RO7247669 dose level (Section 4.3).
- Inclusion criteria have been updated to permit enrollment of locally advanced stage IIIC patients in alignment with most recent 8th edition of the lung cancer UICC/AJCC-staging system (Section 2.1, 2.3, 3, 4.1, 4.2.1, 5.1).
- Inclusion Criteria have been clarified to indicate that a documented local PD-L1 immunohistochemistry assessment of any local health authority approved assay can be used (Section 5.1).
- The exclusion criteria for patients with pulmonary lymphoepithelioma-like carcinoma subtype of NSCLC has been removed in order to align with removal of EBV testing requirements (Section 5.2).
- The exclusion criteria have been updated to specify that patients with known rearranged during transfection mutations will not be permitted to enroll unless ineligible for available targeted therapies. Patients with actionable genomic aberrations should preferentially receive appropriate therapy with targeted treatments when available (Section 5.2).

- Radiographic assessment has been updated with the requirement for a CT scan of the pelvis, to be consistent with the schedule of activities (Section 8.1.1.1).
- The hypothesis testing has been removed as this study is only intended to be hypothesis generating (Section 9.1 and 9.3.1).
- [redacted]
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Appendix 1).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Appendix 1).
- The Sponsor record retention policy has been clarified (Appendix 1).
- Language has been added to clarify that dedicated infusion-related reaction (IRR) eCRFs are necessary to report IRR events (Appendix 3).
- Adverse event management guidelines have been updated to align with the American Society of Clinical Oncology guidelines for management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy (Appendix 6).

PROTOCOL AMENDMENT, VERSION 3: (11 MAY 2023)

Protocol BO44178, Version 3, has been amended to incorporate changes made in Version 1 (United States) of the BO44178 protocol, which was created to address comments from the U.S. Food and Drug Administration. Feedback received from other health authorities has also been addressed. Changes to the protocol, along with a rationale for each change, are summarized below:

- *The protocol has been updated to include the International Nonproprietary Name (INN) of the RO7247669 test compound (tobemstomig) throughout.*
- [redacted]
- *It has been clarified that during survival follow-up, the following patient-reported outcome questionnaires will be completed at 3 months (± 30 days) and 6 months (± 30 days): European Organisation for Research and Treatment of Cancer, IL85, IL132, IL188, and IL17. In addition, the last assessment of the PRO-Common*

Terminology Criteria for Adverse Events (CTCAE) and the single-item EORTC IL46 will be performed at the treatment discontinuation visit (Section 1.3 [Table 1, footnote d]).

- *The Schedule of Activities has been clarified to state that single 12-lead electrocardiograms should be performed in both Cycles 1 and 5, to be consistent with footnote n (Section 1.3 [Table 1]).*
- *For consistency with the inclusion criteria, a footnote has been added to the Schedule of Activities to detail that screening laboratory tests (hematology, serum chemistry panel and coagulation) must be performed within 14 days prior to initiation of study treatment (Section 1.3 [Table 1 (footnote hh)]).*
- *Collection of alcohol use history has been removed as alcohol use history is not a risk factor for NSCLC (Section 1.3 [Table 1 (footnote l)] and Section 8).*
- *Additional guidance for predose sample collection has been added; a 4-hour time window has been added for predose pharmacokinetic, biomarker and immunogenicity sample collection on Day 1 of each cycle (Section 1.3 [Table 2] and Section 8.10.3.3).*
- *Language has been added to define a time window for the collection of biomarker blood (plasma and serum) samples at time of disease progression. Samples should be collected within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner (Section 1.3 [Table 2, footnote g]).*
- *Language has been updated to clarify that EGFR and ALK testing must be performed per the assay's intended use according to local laws and regulations (Sections 1.3, 4.1.1, 4.2.1, 5.2 and 8.7).*
- [redacted]
- *Language has been corrected to reflect that cytokine release syndrome (CRS) events will be graded according to the American Society of Transplantation and Cellular Therapy (ASTCT) CRS Consensus Grading Scale, as opposed to both ASTCT and National Cancer Institute (NCI) CTCAE (Sections 3, 4.1.4 and 9.3.3.5; Appendices A3-2, A3-3.2 and A6-8).*
- *Language has been amended to remove the estimation that there will be approximately 6 months between the date the first participant is randomized and the initial safety run-in evaluation, to allow more flexibility (Section 4.1.3). The initial safety run-in evaluation will take place no later than 6 months after the first participant is randomized.*

- [redacted]
- *An Internal Monitoring Committee (IMC) will perform a cumulative review of safety data approximately every 6 months. However, to ensure patient safety, if 24 participants with non-small cell lung cancer of each histology (squamous or non-squamous) complete two cycles of treatment before a scheduled IMC review, an ad hoc IMC safety review will be added for a safety evaluation (Section 4.1.8).*
- *Language has been added to the rationale for study population to clarify that patients whose tumors have known EGFR mutation or ALK genetic aberrations will be excluded from the study, in order to be consistent with the Schedule of Activities (footnote h) and the eligibility criteria. Patients with tumors of non-squamous histology with unknown EGFR or ALK mutational status will be required to be tested prior to enrollment. Patients with tumors of squamous histology who have an unknown EGFR or ALK mutational status will not be required to be tested at pre-screening/screening (Section 4.2.1).*
- *For consistency with the Schedule of Activities, language has been included to detail that treatment will continue until disease progression per RECIST v1.1, unacceptable toxicity, loss of clinical benefit as determined by the investigator, or until the Sponsor decides to terminate the study, whichever comes first. Additionally, it has been clarified that the total duration of study participation for each individual is expected to range from 1 day to approximately 58 months. Participants will be allowed to continue treatment beyond disease progression if pre-specified criteria are met (Section 4.1.5).*
- *The contraception guidelines have been amended for male patients with either a female partner of childbearing potential who is not pregnant, or a pregnant female partner to state that men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period for 4 months after the final dose of pembrolizumab, to be in line with the prescribing information for pembrolizumab (Sections 5.1 and 8.3.5; Appendix A5-2).*
- *The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in MedDRA (Section 5.2; Appendix 8).*
- *Language has been added to clarify that the first dose of study drug administration should occur within 5 days of randomization (Section 6.3.1).*
- *It has been clarified that Medical Monitor contact information will be provided separately to sites (Section 8.3.9).*
- *The confidence interval range in Table 8 has been corrected to reflect the confidence width of the objective response rate estimated with a targeted sample size of 180 patients (Section 9.1.1).*

- *Language has been added to clarify that the IMC will review both efficacy and safety data during the* [redacted]
- *Language has been added to clarify that microscopic examination of urine samples will only be performed if there is a clinically significant positive dipstick result (confirmed by a repeat positive sample), unless there is an explanation for the positive dipstick result (Appendix A2-1).*
- *The adverse event management guidelines for Grade 3 infusion-related reactions have been revised to permanently discontinue tobemstomig or pembrolizumab to match the current U.S. Prescribing Information for pembrolizumab (Appendix 6 [Table A6-7]).*

Appendix 15
Abbreviations

Abbreviation or Term	Definition
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibody
ALK	anaplastic lymphoma kinase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the concentration–time curve
BEN	benign ethnic neutropenia
BICR	blinded independent central review
BsAb	bispecific antibody
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CPI	checkpoint inhibitor
CrCl	creatinine clearance
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EBUS	endobronchial ultrasound
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
Fc	fragment crystallizable
FDA	(U.S.) Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed, paraffin-embedded
GLP	Good Laboratory Practice
H_0	null hypotheses
H_1	alternative hypothesis
HBcAb	hepatitis B core antibody

Appendix 15: Abbreviations

Abbreviation or Term	Definition
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HLH	hemophagocytic lymphohistiocytosis
HR	hazard ratio
HRQoL	health-related quality of life
IC	immune cell
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IL	Item Library
IM	intramuscular
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive voice or web-based response system
LAG3	lymphocyte activation gene 3
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NSCLC	non–small cell lung cancer
NSQ	non-squamous
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD-1	programmed death–1
PD-L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic

Appendix 15: Abbreviations

Abbreviation or Term	Definition
PO	orally; by mouth
PPD	positive purified protein derivative
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Common Terminology Criteria for Adverse Events
Q3W	every 3 weeks
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RET	rearranged during transfection
ROS1	c-ROS oncogene 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SITC	Society for Immunotherapy for Cancer
SQ	squamous
TB	tuberculosis
[redacted]	
TIL	tumor-infiltrating lymphocyte
TNF	tumor necrosis factor
TnI	troponin I
TnT	troponin T
TPS	tumor proportion score
TTE	transthoracic echocardiogram
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

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