Protocol J2G-MC-JZJC(e)

LIBRETTO-431: A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer

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Title Page

Protocol Title: LIBRETTO-431: A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer

Protocol Number: J2G-MC-JZJC

Amendment: (e)

Compound Number: LY3527723

Study Phase: Phase 3

Short Title: A Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab (LIBRETTO-431)

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 144697

EudraCT: 2019-001979-36

EU trial number: 2023-506783-14-00

Approval Date: Protocol Amendment (e) Electronically Signed and Approved By Lilly on date provided below.

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Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment d	18-Nov-2020
Amendment c	26-Jun-2020
Amendment b	10-Jun-2020
Amendment a	07-Nov-2019
Original Protocol	27-Jun-2019

Amendment (e)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update as per the latest Investigator Brochure (IB) and to align with EU Clinical Trial Regulation (EU-CTR) requirements. In addition, this amendment includes changes made to correct and clarify information for sites. This amendment also corrects typographical errors and inconsistencies that were noted in JZJC amendment(d).

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Added • Regulatory Agency Identifier Number(s) • Study Population • Ethical Considerations of Benefit/Risk	For EU-CTR compliance
	Updated the section to align with the changes in the main body of the protocol	For consistency
1.3. Schedule of Activities (SoA) Baseline, On-Study, and Poststudy Treatment Follow-Up SoA for Patients on Arm A and Arm B	Edited footnote “a” • Footnote clarifying that V201 has no maximum time duration • Clarification around window for baseline crossover imaging	For clarification
1.3. Schedule of Activities (SoA) Optional Crossover Treatment	Clarification around window for the overall screening window	For clarification
5.1. Inclusion Criteria 11. References	Fixed incorrect reference for AJCC Cancer Staging Manual. 8th edition	Correction
6. Study Intervention	Updated the definition of study intervention	For EU-CTR compliance
6.1. Study Intervention(s) Administered	Added last row for “Authorized as defined by EU Clinical Trial Regulation”	For EU-CTR compliance

Section # and Name	Description of Change	Brief Rationale
6.1.2. Packaging and Labeling	Added new section	For EU-CTR compliance
6.6. Dose Modification Guidelines for Arm A and Arm B	• Statement about cycle durations was located in section 6.6.1 but as it applies to both arms, was moved to 6.6 • Table was updated to clarify that 40 mg BID is an acceptable dose for dose reduction • Footnote 'a' was updated	For clarification
6.6.1. Dose Modifications and Toxicity Management Guidelines for Arm A	Corrections made in hypersensitivity dose modification section	Guidance for hypersensitivity recurrence was in the wrong section in previous amendment. Language was also clarified.
	Added updated dose modification guidance for interstitial lung disease/pneumonitis	Updated as per Selpercatinib IB (Aug 2023)
7.1. Discontinuation of Study Intervention	Note regarding approval for continuing study treatment beyond progression was clarified	Clarified to align with Section 8.1.2
8.1.1. Imaging	Added "Section 8.2.2.2 and" to fourth paragraph	For clarification
8.1.2. BICR Assessment	Added language for clarification • Requirement for signing consent in cases of treatment post-progression • Sponsor approval to continue treatment not necessary if BICR does not confirm progression • In crossover, BICR does not provide confirmation of progression	For clarification
8.2.1. Electrocardiograms	Added guidance that if a potential alternative cause for QTcF prolongation is identified, sponsor should be consulted for dose reduction guidance.	For closer sponsor oversight of QTcF prolongation management
8.2.2.2. Chylothorax and Chylous Ascites Monitoring	Added new section	Updated as per Selpercatinib IB (Aug 2023)
8.2.2.3. Renal Safety Monitoring	Added new section	Updated as per Selpercatinib IB (Aug 2023)
8.2.2.4. Thyroid Function Monitoring	Added new section for hypothyroidism to provide additional guidance	Updated as per Selpercatinib IB (Aug 2023)
8.3. Adverse Events and Serious Adverse Events	Added definition and details on adverse events	For EU-CTR compliance
8.3.3. Regulatory Reporting Requirements for SAEs	Updated the section	For EU-CTR compliance
9.4.1. General Statistical Considerations	Added a paragraph on handling of missing, unused, and spurious data	For EU-CTR compliance

Section # and Name	Description of Change	Brief Rationale
10.1.1. Regulatory and Ethical Considerations	Added a bullet point regarding reporting of significant issues related to participant's safety, rights, and data integrity	For EU-CTR compliance
10.1.3. Data Protection	Updated the required language	For EU-CTR compliance
10.1.5. Dissemination of Clinical Study Data	Added paragraph on "Reports"	For EU-CTR compliance
10.5. Appendix 5: Restricted and Prohibited Concomitant Medication	Removed the web reference in footnote	Editorial update
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore, not detailed

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

LIBRETTO-431: A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab as Initial Treatment of Advanced or Metastatic *RET* Fusion-Positive Non-Small Cell Lung Cancer

Short Title: A Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy with or without Pembrolizumab (LIBRETTO-431)

Regulatory Agency Identifier Number(s)

IND: 144697

EudraCT: 2019-001979-36

EU trial number: 2023-506783-14-00

Rationale:

Patients with *RET* fusion-positive non-small cell lung cancer (NSCLC) represent a population with high unmet need. Combination chemotherapy with or without immunotherapy has short-term palliative potential in advanced NSCLC.

The identification of activating genetic alterations in specific tyrosine kinases has led to a new classification of NSCLC based on molecular genotype rather than histology. Agents targeting specific alterations such as *EGFR* and *BRAF* activating mutations and *ALK* and *ROS1* gene fusions have demonstrated compelling efficacy in patients with cancers that harbor the respective activating genetic alteration.

Selpercatinib, a selective RET tyrosine kinase inhibitor, has demonstrated a favorable safety profile and evidence of durable antitumor activity in patients with advanced *RET* fusion-positive patients with NSCLC (both treatment-naïve and those previously treated with approved first-line chemotherapy with or without immunotherapy). As a result, selpercatinib may be of benefit as an initial treatment for advanced or metastatic *RET* fusion-positive NSCLC.

The proposed Study J2G-MC-JZJC (hereafter referred to as JZJC) will evaluate selpercatinib in comparison to platinum-based (carboplatin or cisplatin) and pemetrexed therapy with or without pembrolizumab in patients with locally advanced or metastatic *RET* fusion-positive NSCLC.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare PFS of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) therapy, pemetrexed, and pembrolizumab in patients with advanced or metastatic *RET* fusion-positive NSCLC • To compare PFS of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) and pemetrexed therapy, with or without pembrolizumab, in patients with advanced or metastatic *RET* fusion-positive NSCLC	• PFS per RECIST 1.1 by BICR
Secondary	
• To compare the efficacy of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) therapy, pemetrexed, and pembrolizumab in patients with advanced or metastatic *RET* fusion-positive NSCLC • To compare the efficacy of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) and pemetrexed therapy, with or without pembrolizumab, in patients with advanced or metastatic *RET* fusion-positive NSCLC	• PFS per RECIST 1.1 by investigator • ORR/DOR/DCR per RECIST 1.1 by BICR • ORR/DOR/DCR per RECIST 1.1 by investigator • Intracranial ORR/DOR per RECIST 1.1 by BICR • Time to CNS progression per RECIST 1.1. by BICR • Intracranial ORR/DOR per RANO-BM by BICR • OS • PFS2 • Time to deterioration in pulmonary symptoms: cough, chest pain, and dyspnea as measured by the NSCLC-SAQ
• To assess safety and tolerability of selpercatinib compared to platinum-based and pemetrexed therapy with pembrolizumab • To assess safety and tolerability of selpercatinib compared to platinum-based and pemetrexed therapy with or without pembrolizumab	• Including but not limited to SAEs, AEs, deaths, and clinical laboratory abnormalities per CTCAE v5.0
• To assess/evaluate performance of *RET* local laboratory tests compared to a single, central test	• *RET* fusion status

Abbreviations: AE = adverse event; BICR = blinded independent central review; CNS = central nervous system; CTCAE = Common Terminology Criteria in Adverse Events; DCR = disease control rate; DOR = duration of response; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases; RECIST 1.1= Response Evaluation Criteria in Solid Tumors, version 1.1; SAE = serious adverse event.

Overall Design:

Study JZJC is a global, multicenter, randomized, open-label, controlled Phase 3 study of selpercatinib (Arm A) compared to platinum-based and pemetrexed therapy with or without pembrolizumab (Arm B) in patients with locally advanced or metastatic, *RET* fusion-positive nonsquamous NSCLC. Enrolled patients will be stratified based on geography (East Asia vs. non-East Asia), brain metastases per investigator assessment (presence vs. absence or unknown), and investigator's choice of treatment if randomized to Arm B (with or without pembrolizumab and cisplatin vs. carboplatin – choice/intent of treatment regimen must be declared prior to randomization). Patients will be randomized in a ratio of 2:1, Arm A to Arm B. Patients will be allowed cross over from the comparator Arm B to Arm A upon confirmation of disease progression by a blinded independent central review if they meet the eligibility criteria for crossover. The primary endpoint being evaluated is PFS per RECIST 1.1 by BICR.

Study Population

- Stage IIIB-IIIC or Stage IV NSCLC that is predominantly nonsquamous in histology.
- Must have a *RET* gene fusion in tumor using polymerase chain reaction (PCR) or next generation sequencing (NGS). Results in blood using NGS are also acceptable.
- Must have measurable disease per RECIST 1.1.
- Must have Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2.
- Must not have received prior systemic therapy for metastatic disease
- Must not have additional validated oncogenic drivers in NSCLC, if known
- Must not have symptomatic central nervous system (CNS) metastases

Disclosure Statement: This is a randomized, active treatment study with 2 arms where the participant and investigator will not be blinded, but the aggregate data in the clinical research database will be blinded to sponsor personnel.

Number of Participants:

Approximately 250 participants will be randomly assigned to study intervention (approximately 167 patients in the experimental arm vs. approximately 83 patients in the control arm).

Intervention Groups and Duration:

	Arm A (Selpercatinib)	**Arm B** (Investigator's discretion of carboplatin or cisplatin + pemetrexed ± pembrolizumab)			
Intervention	Selpercatinib	Carboplatin	Cisplatin	Pemetrexed	Pembrolizumab (investigator's choice)
Dose	160 mg	AUC 5 (maximum dose 750 mg)	75 mg/m^2	500 mg/m^2 (with vitamin supplementation)	200 mg
Schedule	BID in 21-day continuous cycles	Day 1 Q3W for 4 cycles	Day 1 Q3W for 4 cycles	Day 1 Q3W	Day 1 Q3W up to 35 cycles
Route	Oral	IV	IV	IV	IV
Authorized as defined by EU Clinical Trial Regulation	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Authorized and used according to EU authorization

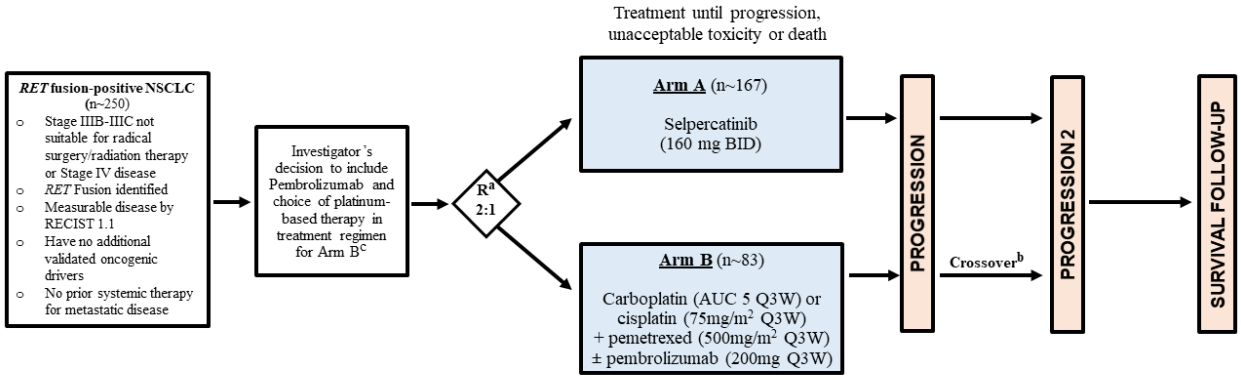
Abbreviations: AUC = area under the concentration versus time curve; BID = twice a day; IV = intravenous; m = meter; mg = milligrams; Q3W = every 3 weeks.

Ethical Considerations of Benefit/Risk:

The need for targeted therapies to treat *RET* fusion-positive NSCLC and the clinical safety and efficacy profile of selpercatinib in patients with *RET*-altered solid tumors (including NSCLC) in the ongoing Phase 1/2 trial (LIBRETTO-001), the risk/benefit assessment supports evaluation of selpercatinib in the proposed patient population.

Data Monitoring Committee: Yes

1.2. Schema



STUDY OBJECTIVES AND ENDPOINT	
Primary Objectives	• To compare PFS of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) therapy, pemetrexed and pembrolizumab • To compare PFS of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) therapy, pemetrexed therapy, with or without pembrolizumab
Primary Endpoint	• PFS per RECIST 1.1 by BICR

Abbreviations: AUC = area under the concentration versus time curve; BICR = blinded independent central review; BID = twice a day; m = meter; mg = milligrams; n = number of participants; NSCLC = non-small cell lung cancer; PFS = progression-free survival; Q3W = every 3 weeks; R = randomization; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.

a Stratification factors: geography (East Asia vs. non-East Asia), brain metastases per investigator assessment (presence vs. absence or unknown), and investigator's choice of treatment if randomized to Arm B (with or without pembrolizumab– choice/intent of treatment regimen must be declared prior to randomization).

b To Arm A (selpercatinib) allowed at radiographic disease progression confirmed by BICR.

c Patients with the intent by the investigator to be treated without pembrolizumab will be restricted to 20%.

1.3. Schedule of Activities (SoA)

This section includes the following SoAs:

- Prescreening
- Baseline, On-Study, and Poststudy Treatment Follow-Up SoA for Patients on Arm A and Arm B
- Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)
- Continued Access SoA for All Patients

Prescreening

Visit	Prescreening	Instructions
Prescreening ICF	X	In geographies or sites where *RET* testing is not standard of care and/or an acceptable local test (as defined by Lilly) is not available, a prescreening consent may be used to provide information to the patient regarding testing to determine tumor *RET* status. The results may also include other genes (e.g. EGFR, ALK, ROS1, KRAS, BRAF, HER2, MET, NTRK1, NTRK2, or NTRK3). If it is considered safe to perform, patients who do not have sufficient available tumor tissue may undergo a fresh tumor biopsy/FNA to determine initial eligibility.

Abbreviation: FNA = fine needle aspiration; ICF = informed consent form.

Baseline, On-Study, and Poststudy Treatment Follow-Up SoA for Patients on Arm A and Arm B

Study Period	**Baseline**		**Study Treatment (Cycle = 21 days)**						**Safety assessments prior to crossover (only for patients on Arm B)**		**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**			**Cycle 2-n**			**V201[a]**		**V801: Short-Term Follow-up[a]**	**V802-X: Long-Term Follow-up[b]**	
Visit Duration/Window	Up to 28 days		-3 days	±3 days	±3 days	±3 days	±3 days	±3 days	1-30 (±7 days)	1-x days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
Informed consent	X												ICF must be signed before any protocol-specific procedures are performed. See Appendix 1.
Inclusion/exclusion criteria	X												See Section 5.
Medical history	X												Including assessment of pre-existing conditions, historical illnesses, prior anticancer therapy, and habits (e.g., smoking status).
Confirm acceptability of local *RET* assessment	X												The test may have occurred prior to consent. Lilly must confirm acceptability of results, preferably and if feasible, prior to conducting other screening procedures. Molecular report(s) describing *RET* and other alterations must be submitted for review (see Section 8.8).
Local PD-L1 assessment	X												Submit if PD-L1 status is known, preferably prior to enrollment. The test may have occurred prior to consent.
Archived tumor tissue or fresh biopsy	See Instructions												If available, this sample should be submitted as described in Section 8.8.1, preferably within 30 days of C1D1. A single sample submitted outside of the 30-day window will not be

Study Period	**Baseline**		**Study Treatment (Cycle = 21 days)**						**Safety assessments prior to crossover (only for patients on Arm B)**		**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**			**Cycle 2-n**			**V201[a]**		**V801: Short-Term Follow-up[a]**	**V802-X: Long-Term Follow-up[b]**	
Visit Duration/Window	Up to 28 days		-3 days	±3 days	±3 days	±3 days	±3 days	±3 days	1-30 (±7 days)	1-x days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
													considered a protocol deviation. Please submit sample from the most recent biopsy with adequate tissue.
Optional postprogression tumor biopsy									X		See Instructions		Can be obtained any time prior to the start of next therapy
Concomitant medication	X		X						X		X		Record prior and concurrent medications at baseline. Record all premedication, supportive care, and concomitant medication throughout the study.
Physical examination		X	X			X			X		X		Physical examination and review of relevant systems at Screening. Symptom-directed physical examinations may be performed at other time points.
Height, weight, and vital signs		X	X			X			X		X		Includes height (only at baseline), weight, blood pressure, pulse rate, pulse oximetry, and temperature. All patients should have their blood pressure optimized (if necessary) prior to initiation of study drug to a reading of ≤140/90 mmHg.

Study Period	**Baseline**		**Study Treatment (Cycle = 21 days)**						**Safety assessments prior to crossover (only for patients on Arm B)**		**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**			**Cycle 2-n**			**V201[a]**		**V801: Short-Term Follow-up[a]**	**V802-X: Long-Term Follow-up[b]**	
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Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
ECG	X		X	X		See Instructions							Obtain triplicate local ECGs at Screening, C1D1, C1D8, and C2-6D1. For Arm A patients, it is preferable to obtain approximately 2 hours after the morning dose. For Arm B patients, obtain following the last infusion. See Section 8.2.1 for additional information, including requirements for potential adjudication.
ECOG performance status		X	X			X			X		X		
Karnofsky performance scale		X	X			X			X		X		For RANO-BM assessment.
AE collection	X		X						X		X		Collect throughout the study. Use CTCAE Version 5.0. All SAEs (regardless of causality) should be reported for 90 days from the last dose of study drug (or until a new therapy starts). After 90 days, only SAEs related to study treatment or protocol procedures are reported in long-term follow-up.
Radiologic imaging and measurement of palpable or visible lesions (X-ray, CT scan with bone	X					See Instructions			X		X		Perform assessments at 6 weeks (±7 days) and 12 weeks (±7 days) and then every 9 weeks (±7 days) for the first 48 weeks following C1D1 and then every 12 weeks (±7 days)

Study Period	**Baseline**		**Study Treatment (Cycle = 21 days)**						**Safety assessments prior to crossover (only for patients on Arm B)**		**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**			**Cycle 2-n**			**V201[a]**		**V801: Short-Term Follow-up[a]**	**V802-X: Long-Term Follow-up[b]**	
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Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
windows, MRI, bone scintigraphy, PET scan or PET component of PET/CT scan)													thereafter until progression, the start of a new anticancer therapy, death, or study completion. For patients with nonmeasurable bone disease bone scintigraphy (preferred) or PET scan or PET component of PET/CT scan may be obtained every 24 weeks (±7 days) or more often if clinically indicated. The scanning interval should be maintained even if cycles are delayed. As a result, the scans may not always occur at the end of a cycle. See Section 8.1.
Intracranial evaluation with CT or MRI	X					See Instructions			X		X		Required for all patients. Should be obtained at baseline and then at the same frequency as other radiologic imaging and as clinically indicated. See Section 8.1.
Submit scans	X					See Instructions			X		X		All scans taken for tumor assessment (e.g., radiographic, bone, and intracranial) should be submitted to Lilly's designee within 5 business days of collection for central review by the BICR. A single scan sent outside the assessment windows will not be considered a protocol deviation, but repeated

Study Period	**Baseline**		**Study Treatment (Cycle = 21 days)**						**Safety assessments prior to crossover (only for patients on Arm B)**		**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**			**Cycle 2-n**			**V201[a]**		**V801: Short-Term Follow-up[a]**	**V802-X: Long-Term Follow-up[b]**	
Visit Duration/Window	Up to 28 days		-3 days	±3 days	±3 days	±3 days	±3 days	±3 days	1-30 (±7 days)	1-x days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
													excursions may be, unless approval has been obtained from the Sponsor.
Pregnancy test		X	See Instructions						X		X	See Instructions	Applies only to women of childbearing potential. Perform within 24 hours prior to the first dose of study drug. Notes: • During study treatment, perform at least monthly or as required per local regulations and/or institutional guidelines. See Appendix 2. • Only patients on pembrolizumab require a pregnancy test approximately 120 days poststudy treatment discontinuation.
Hematology		X	See Instructions	X	X	X			X		X		If screening testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. Additional assessments may be obtained at the discretion of the investigator. See Appendix 2.
Coagulation		X	X										If baseline testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. Additional assessments may be obtained at the discretion of the investigator. See

Study Period	**Baseline**		**Study Treatment (Cycle = 21 days)**						**Safety assessments prior to crossover (only for patients on Arm B)**		**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**			**Cycle 2-n**			**V201[a]**		**V801: Short-Term Follow-up[a]**	**V802-X: Long-Term Follow-up[b]**	
Visit Duration/Window	Up to 28 days		-3 days	±3 days	±3 days	±3 days	±3 days	±3 days	1-30 (±7 days)	1-x days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
													Appendix 2.
Urinalysis		X	X			See Instructions			X		X		If baseline testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. For Cycles 2-n, as clinically indicated. See Appendix 2.
Clinical chemistry		X	See Instructions	X		X			X		X		If baseline testing is performed ≤7 days prior to C1D1, repeat testing does not need to occur on C1D1. Should be performed on D1 of every subsequent cycle (e.g., C2D1, C3D1). Additional assessments may be obtained at the discretion of the investigator. See Appendix 2.
Routine hepatic safety monitoring					X			See Instructions					Including AST, ALT, total/direct bilirubin, and ALP. Should be performed on C1D15, C2D15, and C3D15. Additional assessments may be obtained at the discretion of the investigator
Thyroid function		X				See Instructions			X		X		Starting in Cycle 2 and every other cycle for the first 8 cycles (e.g., Cycles 2, 4, 6, 8). Thereafter should be collected at the investigator's discretion. Patients receiving pembrolizumab should continue to be monitored every other cycle. See Appendix 2.

Study Period	**Baseline**		**Study Treatment (Cycle = 21 days)**						**Safety assessments prior to crossover (only for patients on Arm B)**		**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**			**Cycle 2-n**			**V201[a]**		**V801: Short-Term Follow-up[a]**	**V802-X: Long-Term Follow-up[b]**	
Visit Duration/Window	Up to 28 days		-3 days	±3 days	±3 days	±3 days	±3 days	±3 days	1-30 (±7 days)	1-x days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
Plasma for cfDNA analysis and exploratory biomarkers			X (Predose)		X	X			X		X		
Whole blood for genomic DNA			X										Sample can be collected at any time if not collected on C1D1.
Blood sample for pharmacokinetics				X		X							Arm A only: Samples to be drawn prior to the morning dose (-2 to 0 hr) in Cycles 1 to 6. See Section 8.5.
Survival and PFS2 information											X		Survival information may be collected by contacting the patient or family directly (e.g., via telephone) if no procedures are required. This information should be collected approximately every 90 days from the end of short-term follow up. See Section 8.1.
Collection of poststudy treatment anticancer therapy information											X		Perform every 90 days from the end of short-term follow up for the first 2 years after discontinuation from study treatment and approximately every 6 months thereafter until death or study completion.

Study Period	Baseline		Study Treatment (Cycle = 21 days)						Safety assessments prior to crossover (only for patients on Arm B)		Poststudy Treatment Discontinuation		Instructions
Cycle/Visit	Screening		Cycle 1			Cycle 2-n			V201[a]		V801: Short-Term Follow-up[a]	V802-X: Long-Term Follow-up[b]	
Visit Duration/Window	Up to 28 days		-3 days	±3 days	±3 days	±3 days	±3 days	±3 days	1-30 (±7 days)	1-x days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
EORTC QLQ-C30			X			X			X		X		The patient will complete electronically at the clinic site. Please collect at C1-n, D1 prior to study intervention. If the patient completed their 30-day assessments (V201) and discontinue prior to crossing over, they will not need to complete the Visit 801 assessments. For the long-term follow-up collection, please collect until disease progression. See Section 8.9.
EORTC IL19			X	X	X	X	X	X					The patient will complete electronically on the provided electronic device at home (not at the site). Items 1 to 5 of the EORTC IL19 will be collected. See Section 8.9.
NSCLC-SAQ			X	X	X	X	X	X					The patient will complete electronically on the provided electronic device at home (not at the clinic site, except C1D1). Please collect at C1D1 prior to study intervention. See Section 8.9.

Study Period	**Baseline**		**Study Treatment (Cycle = 21 days)**						**Safety assessments prior to crossover (only for patients on Arm B)**		**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**			**Cycle 2-n**			**V201[a]**		**V801: Short-Term Follow-up[a]**	**V802-X: Long-Term Follow-up[b]**	
Visit Duration/Window	Up to 28 days		-3 days	±3 days	±3 days	±3 days	±3 days	±3 days	1-30 (±7 days)	1-x days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
PRO-CTCAE			X	X	X	X	X	X					The patient will complete electronically on the provided electronic device at home (not at the clinic site, except C1D1). Selected items will be collected. Please collect at C1D1 prior to study intervention. See Section 8.9.
FACT-GP5			X	X	X	X	X	X					The patient will complete electronically on the provided electronic device (not at the clinic site, except C1D1). Please collect at C1D1 prior to study intervention. See Section 8.9.
EQ-5D-5L			X			X			X		X	X	The patient will complete electronically at the clinic site. Please collect at C1-n, D1 prior to study intervention. If the patient completed their 30 day assessments (V201) and discontinued prior to crossing over, they will not need to complete the Visit 801 assessment. For the long-term follow-up collection, please collect until disease progression. In Long-term follow-up completion is only required if the patient is physically in clinic (e.g. for radiographic assessment). See Section 8.9.
Patient dosing diary			X										For Patients on Arm A: Provide patient diary Day 1.

Study Period	**Baseline**		**Study Treatment (Cycle = 21 days)**						**Safety assessments prior to crossover (only for patients on Arm B)**		**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening**		**Cycle 1**			**Cycle 2-n**			**V201[a]**		**V801: Short-Term Follow-up[a]**	**V802-X: Long-Term Follow-up[b]**	
Visit Duration/Window	Up to 28 days		-3 days	±3 days	±3 days	±3 days	±3 days	±3 days	1-30 (±7 days)	1-x days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤28	≤14	D1	D8	D15	D1	D8	D15	N/A	N/A	N/A	N/A	
Procedure													
													Completed daily by patient. Review at each study visit.
Dispense selpercatinib			X										For Patients on Arm A. See Section 6.1.
Premedication		X	X			X							As appropriate for the therapy (e.g., folic acid, B12, dexamethasone prior to pemetrexed therapy) and following local practice and labels. See Section 6.1.
Administer cisplatin or carboplatin			X			X							See Section 6.1.
Administer pemetrexed			X			X							See Section 6.1.
Administer pembrolizumab			X			X							See Section 6.1.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BICR = blinded independent central review; C = cycle; cfDNA = circulating cell-free DNA; CNS = central nervous system; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0; EORTC IL19 = European Organisation for Research and Treatment of Cancer Item library 19; EQ-5D-5L = EuroQol Five Dimension Five Level; FACT-GP5 = Functional Assessment of Cancer Therapy-Side Effects; hr = hour; ICF = informed consent form; MRI = magnetic resonance imaging; N/A = not applicable; NSCLC-SAQ = Non-Small Cell Lung Cancer-Symptom Assessment Questionnaire; PD-L1 = programmed death-ligand 1; PET = positron emission tomography; PFS2 = progression-free survival 2; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases; SAE = serious adverse event; SoA = Schedule of Activities; V = visit.

[a] Short-term follow-up begins when the patient and investigator agree that the patient will no longer continue study treatment:

- All patients in Part A should complete V801 and will not complete V201.
- Patients in Arm B that may potentially crossover will enter V201.
    - V201 has no maximum time duration.
    - Patients in Arm B who will crossover to selpercatinib more than 37 days (30 days +/- 7days) after the last dose of study treatment should complete V201 assessments. If a patient in V201 that has completed the V201 assessments does not enter crossover (V300), they do not need to complete the V801 assessments, but will need to complete V802 assessments.
    - Patients in Arm B who will crossover to selpercatinib in 37 days or less should discontinue from V201 when the decision to be screened for crossover is made. They will not complete the V201 assessments, but rather enter visit 300 and complete the screening assessments for crossover.
    - Patients in Arm B who will not potentially crossover to selpercatinib should not enter V201. They will not complete the V201 assessments, but rather subsequently enter V801 and complete the V801 assessments.

[b] Long-term follow-up begins when short-term follow-up period is completed and continues until death, study withdrawal, or the patient is lost to follow-up. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Note: Baseline/screening assessments and laboratory values drawn within the indicated window of C1D1 may be used for both screening/baseline and C1D1 assessments. There is not a defined interval required from randomization to C1D1.

Optional Crossover Treatment (for patients crossing over from Arm B to Arm A)

Applicable only for patients initially randomly assigned to Arm B (platinum-based therapy with pemetrexed with or without pembrolizumab) who have progression that is confirmed by the blinded independent central review (BICR) and who are eligible for crossover treatment.

Study Period	**Crossover Baseline**		**Study Treatment (Cycle = 21 days)**						**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening (V300)**		**Cycle 301**			**Cycle 302-n**			**Short-Term Follow-up[a]**	**Long-Term Follow-up[b]**	
Visit duration/window	Up to 42 days		-3 days	±3 days	±3 days	± 3 days	±3 days	±3 days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤42	≤14	D1	D8	D15	D1	D8	D15	V801	V802-X	
Procedure											
Informed consent	X										ICF must be signed before any protocol-specific procedures are performed. See Appendix 1.
Inclusion/exclusion criteria for crossover phase		X									See Section 5.2.2.
Optional postprogression tumor biopsy									See Instructions		Can be obtained any time prior to the start of next therapy
Concomitant medication	X		X						X		Record all premedication, supportive care, and concomitant medication throughout crossover treatment.
Physical examination		X	X			X			X		Physical examination and review of relevant systems at Screening. Symptom-directed physical examinations, including measurement of weight may be performed at other time points.
Weight and vital signs		X	X			X			X		Includes weight, blood pressure, pulse rate, pulse oximetry, and temperature. Can be done at C301D1. All patients should have their blood pressure optimized (if necessary) prior to initiation of study drug to a reading of ≤140/90 mmHg.
ECG		X	X	X		See Instructions					Obtain triplicate local ECGs at Screening, C301D1, C301D8, and C302-6D1. It is preferable to obtain approximately 2 hours after dosing. See Section 8.2.1 for additional information, including requirements for potential adjudication.

Study Period	Crossover Baseline		Study Treatment (Cycle = 21 days)						Poststudy Treatment Discontinuation		Instructions
Cycle/Visit	**Screening (V300)**		**Cycle 301**			**Cycle 302-n**			**Short-Term Follow-up[a]**	**Long-Term Follow-up[b]**	
Visit duration/window	Up to 42 days		-3 days	±3 days	±3 days	± 3 days	±3 days	±3 days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤42	≤14	D1	D8	D15	D1	D8	D15	V801	V802-X	
Procedure											
ECOG performance status		X	X			X			X		
Karnofsky performance scale		X	X			X			X		For RANO-BM assessment.
AE collection	X		X						X		Collect throughout Crossover Treatment. Use CTCAE Version 5.0. Only SAEs related to study treatment or protocol procedures are reported in long-term follow-up.
Radiologic imaging and measurement of palpable or visible lesions (X-ray, CT scan with bone windows, MRI, bone scintigraphy [preferred], PET scan or PET component of PET/CT scan)	See Instructions					See Instructions			X		Perform within 35 days prior to the first dose of selpercatinib in the crossover period. Perform assessments at 6 weeks (±7 days) and 12 weeks (±7 days) and then every 9 weeks (±7 days) for the first 48 weeks following C301D1 and then every 12 weeks (±7 days) thereafter until progression, the start of a new anticancer therapy, death, or study completion. For patients with nonmeasurable bone disease bone scintigraphy (preferred) or PET scan or PET component of PET/CT scan may be obtained every 24 weeks (±7 days) or more often if clinically indicated. Scans obtained prior to the signing of the crossover consent may be used. See Section 8.1.
Intracranial evaluation with CT or MRI	See Instructions					See Instructions			X		Required for all patients. Should be obtained at baseline and then at the same frequency as other radiologic imaging and as clinically indicated. See Section 8.1.
Submit scans	X					See Instructions			X		All scans taken for tumor assessment (e.g., radiographic, bone, and intracranial) should be submitted to Lilly's designee for central review by the BICR.
Pregnancy test		X	See Instructions						X		Perform within 24 hours prior to the first dose of selpercatinib in the crossover period. Applies only to women of childbearing potential. Note: during study treatment, perform at least monthly or as required per local regulations and/or institutional guidelines. See Appendix 2.

Study Period	**Crossover Baseline**		**Study Treatment (Cycle = 21 days)**						**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening (V300)**		**Cycle 301**			**Cycle 302-n**			**Short-Term Follow-up[a]**	**Long-Term Follow-up[b]**	
Visit duration/window	Up to 42 days		-3 days	±3 days	±3 days	± 3 days	±3 days	±3 days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤42	≤14	D1	D8	D15	D1	D8	D15	V801	V802-X	
Procedure											
Hematology		X	X	X	X	X			X		Additional assessments may be obtained at the discretion of the investigator. See Appendix 2.
Coagulation		X	X								Additional assessments may be obtained at the discretion of the investigator. See Appendix 2.
Urinalysis		X	X			See Instructions			X		For Cycles 302-n, as clinically indicated for subsequent cycles. See Appendix 2.
Clinical chemistry		X	X	X		X			X		Should be performed on C302D1, C303D1, and then D1 of every subsequent cycle (e.g., C302, C303). Additional assessments may be obtained at the discretion of the investigator. See Appendix 2.
Hepatic monitoring					X			See Instructions			Including AST, ALT, total/direct bilirubin, and ALP. Should be performed on C301D15, C302D15, and C303D15. Additional assessments may be obtained at the discretion of the investigator
Thyroid function		X				See Instructions					Starting in Cycle 302 and every other cycle for the first 8 cycles (e.g., Cycles 2, 4, 6, 8). Thereafter should be collected at the investigator's discretion. See Appendix 2.
Plasma for cfDNA analysis and exploratory biomarkers			X (pre-dose)		X	X			X		
Blood sample for pharmacokinetics				X		X					Samples to be drawn prior to the morning dose (-2 to 0 hr) in Cycles 301 to 306. See Sections 8.5 and 8.6.
Survival information									X		Survival information may be collected by contacting the patient or family directly (e.g., via telephone) if no procedures are required. This should be collected approximately every 90 days from the end of short-term follow up.
Collection of poststudy-treatment anticancer therapy information									X		Perform every 90 days from the end of short-term follow up for the first 2 years after discontinuation from study treatment and every 6 months (±14 days) thereafter until death or study completion.

Study Period	**Crossover Baseline**		**Study Treatment (Cycle = 21 days)**						**Poststudy Treatment Discontinuation**		**Instructions**
Cycle/Visit	**Screening (V300)**		**Cycle 301**			**Cycle 302-n**			**Short-Term Follow-up[a]**	**Long-Term Follow-up[b]**	
Visit duration/window	Up to 42 days		-3 days	±3 days	±3 days	± 3 days	±3 days	±3 days	30±7 days	90±7 days	
Relative Day within Dosing Cycle	≤42	≤14	D1	D8	D15	D1	D8	D15	V801	V802-X	
Procedure											
EORTC QLQ-C30			X			X			X		The patient will complete electronically at the clinic site. See Section 8.9.
EORTC IL19			X	X	X	X	X	X			The patient will complete electronically on the provided electronic device at home (not at the clinic site). Items 1 to 5 of the IL19 will be collected. See Section 8.9.
NSCLC-SAQ			X	X	X	X	X	X			The patient will complete electronically on the provided electronic device at home (not at the clinic site). See Section 8.9.
PRO-CTCAE			X	X	X	X	X	X			The patient will complete electronically on the provided electronic device at home (not at the clinic site). Selected items will be collected. See Section 8.9.
FACT-GP5			X	X	X	X	X	X			The patient will complete electronically on the provided electronic device at home (not at the clinic site). See Section 8.9.
EQ-5D-5L			X			X			X	X	The patient will complete electronically at the clinic site. In Long-term follow-up, completion is only required if the patient is physically in clinic (e.g. for radiographic assessment). See Section 8.9.
Premedication			X			X					As appropriate for the therapy and following local practice and labels. See Section 6.1.
Patient dosing diary			X								Provide patient diary Day 1. Completed daily by patient. Review at each study visit.
Dispense selpercatinib			X								See Section 6.1.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BICR = blinded independent central review; C = cycle; cfDNA = circulating cell-free DNA; CNS = central nervous system; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0; EORTC IL19 = European Organisation for Research and Treatment of Cancer, item library 19; EQ-5D-5L = EuroQol Five Dimension Five Level; FACT-GP5 = Functional Assessment of Cancer Therapy-Side Effects; hr = hour; ICF = informed consent form; MRI = magnetic resonance imaging; NSCLC-SAQ = Non-small Cell Lung Cancer-Symptom Assessment Questionnaire; PET = positron emission tomography; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases; SAE = serious adverse event; V = visit.

[a] Short-term follow-up begins when the patient and investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days).

[b] Long-term follow-up begins when short-term follow-up period is completed and continues until death, study withdrawal, or the patient is lost to follow-up. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

Note: Crossover baseline/screening assessments and laboratory values drawn within the indicated window of C301D1 may be used for both crossover screening/baseline and C301D1 assessments.

Continued Access SoA for All Patients

Visit	Study Treatment	30-Day Follow-Up[a]	Instructions
	501-5XX	901	
Procedure[b]			
AE collection	X	X	Per CTCAE v5.0., for posttreatment follow-up, the investigator should only collect SAEs related to the study treatment regimen or protocol procedures. Collect throughout the study.
Administer study intervention	X		See Section 6.1 for Study Intervention administration details and guidelines.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event.

a Continued access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

b Efficacy assessments will be done at the investigator's discretion based on the standard of care.

2. Introduction

2.1. Study Rationale

Patients with *RET* fusion-positive non-small cell lung cancer (NSCLC) represent a population with high unmet need. Combination chemotherapy has short-term palliative potential in advanced NSCLC. While antiprogrammed cell death protein 1 (anti-PD-1) monoclonal antibodies (e.g., nivolumab and pembrolizumab) have extended progression-free survival (PFS) and recently been approved for patients with NSCLC in some geographies, they may be less effective as monotherapy in tumors marked by single-gene driver oncogenic kinase alterations (including kinase fusions) with otherwise low mutation burdens and low neoantigen production (Borghaei et al. 2015; Rizvi et al. 2015; Gainor et al. 2016; Herbst et al. 2016).

Agents targeting specific alterations such as *EGFR* and *BRAF* activating mutations and *ALK* and *ROS1* gene fusions have demonstrated compelling efficacy in patients with cancers that harbor the respective activating genetic alteration (Lindeman et al. 2018; Pakkala and Ramalingam 2018).

Selpercatinib, a selective RET tyrosine kinase inhibitor (TKI), has demonstrated a favorable safety profile and evidence of durable antitumor activity in patients with advanced *RET* fusion-positive NSCLC (both treatment naïve and those previously treated with approved first-line chemotherapy with or without immunotherapy [Drilon et al. 2018; Oxnard et al. 2018, Wirth et al. 2018]). As a result, selpercatinib may be of benefit as an initial treatment with advanced or metastatic *RET* fusion-positive NSCLC.

2.2. Background

Lung cancer is the most common form of cancer and the most common cause of cancer deaths worldwide, with 2.09 million new cases and 1.76 million deaths in 2018. Approximately 80% to 85% of lung cancers are NSCLCs (American Lung Association 2019, Lung Cancer Fact Sheet).

Standard of care (SOC) first-line treatment for patients with NSCLC remains, in most cases, platinum-based chemotherapy regimens. Typical response rates to platinum-based therapies are 20% to 30%, with a median PFS (mPFS) of approximately 5 months (Paz-Ares et al. 2018). Recent studies have demonstrated that addition of an immune checkpoint inhibitor (e.g., anti-PD-1 or PD-L1 antibody) to platinum-based regimens will improve responses and PFS. As an example, patients treated with the combination of pembrolizumab plus pemetrexed plus platinum demonstrated better outcomes compared to those treated with control arm of pemetrexed plus platinum in response rates (47.6% vs. 18.9%), PFS (8.8 months vs. 4.9 months), and overall survival (OS) (not reached vs. 11.3 months [Gandhi et al. 2018]), respectively. The benefits were observed regardless of PD-L1 status. For patients with high PD-L1 expression (tumor proportion score [TPS] of 50% or greater), monotherapy with a PD-L1 inhibitor may be sufficient (Reck et al. 2016): in a randomized Phase 3 trial, patients treated with pembrolizumab monotherapy achieved better outcomes compared to those treated with chemotherapy (mPFS of 10.3 months vs. 6.0 months, respectively; hazard ratio [HR] 0.50). Recent data indicate that immune checkpoint inhibitors may be less effective in patients with oncogenic driver-positive NSCLC, including patients with *RET* alterations.

The identification of mutually exclusive, activating genetic alterations in specific tyrosine kinases has led to a new classification of NSCLC based on molecular genotype rather than histology. Matching a specific targeted TKI to the specific driver mutation identified has led to a paradigm shift in the treatment of NSCLC, with targeted therapy considered the preferred initial treatment for patients with NSCLC with *EGFR* and *BRAF* activating mutations and *ALK* and *ROS1* gene fusions, and chemotherapy and immunotherapy saved for later lines of therapy. Molecular profiling of NSCLC tumors is recommended by international consensus guidelines as part of routine evaluation in newly diagnosed patients to identify these known driver mutations (*EGFR*, *ALK*, and *ROS1*) as well as a second group of genes that should be included in any expanded panel that is offered for lung cancer patients including *BRAF*, *MET*, *RET*, *ERBB2 (HER2)*, and *KRAS* (Lindeman et al. 2018).

Given the high efficacy and differentiated toxicity (compared to platinum-based chemotherapy regimens) observed for these TKIs, ongoing clinical trials are examining whether newer selective TKIs can also benefit patients with NSCLC whose cancers harbor activating genetic alteration in other kinases (Mok et al. 2009; Zhang et al. 2017). The *RET* receptor tyrosine kinase is oncogenically activated by chromosomal rearrangements producing *RET* gene fusions in 1% to 2% of patients with NSCLC (Ju et al. 2012; Kohno et al. 2012; Lipson et al. 2012; Takeuchi et al. 2012; Kato et al. 2016). Several multikinase inhibitors (MKI) with some degree of anti-RET activity and approved for other cancers demonstrated modest activity in *RET* fusion-positive lung cancer in Phase 2 studies, with response rates of 16% to 53% (depending on the specific MKI and patient population), but PFS of only 3.6 to 7.3 months (Drilon et al. 2018; Oxnard et al. 2018; Wirth et al. 2018). The efficacy of these MKIs in patients is ultimately limited by incomplete inhibition of *RET* in tumors, significant toxicity from stronger inhibition of other targets (e.g., *KDR/VEGFR2*, *EGFR*, and *MET*), and poor pharmacokinetics (PK) (i.e., significant drug accumulation and long half-life contributing to toxicity but not efficacy). As a result, most patients treated with these agents experience significant toxicities requiring dose interruptions, reductions, and/or treatment cessation.

Selpercatinib is a highly potent and specific small-molecule inhibitor of the RET kinase, with minimal inhibition of other kinase and nonkinase targets. A Phase 1/2 study (Drilon et al. 2018; Oxnard et al. 2018; Wirth et al. 2018) was designed to assess the safety, PK, and antitumor activity of selpercatinib in patients with *RET*-altered solid tumors. The Phase 1 portion of the study has been completed and the Phase 2 portion is currently ongoing. The recommended Phase 2 dose was established as 160 mg twice a day (BID). Please see the Investigator's Brochure (IB) for the most current safety information.

As of 30 March 2019, 422 patients were enrolled in Study LOXO-RET-17001 (LIBRETTO-001) and received treatment with selpercatinib across 9 dose levels ranging from 20 mg once daily (QD) to 240 mg BID, treatment-emergent adverse events (TEAEs) occurring in ≥15% patients were dry mouth (30.8%), diarrhea (27.7%), hypertension (27.3%), fatigue (22.3%), constipation (21.8%), aspartate aminotransferase (AST) increased (21.6%), alanine aminotransferase (ALT) increased (20.4%), headache (18.7%), nausea (18.0%), edema peripheral (17.3%), and blood creatinine increased (14.9%).The most common Grade ≥3 TEAEs included hypertension (12.3), ALT increased (6.2%), AST increased (4.7%), hyponatremia (4.3%), electrocardiogram (ECG) QT prolonged (2.8%), dyspnea and lymphopenia (each 2.6%), and diarrhea and thrombocytopenia (each 2.1%).All other Grade ≥3 TEAEs occurred in less than 2% of patients overall. During dose escalation, 2 dose-limiting toxicities (DLTs) were reported, both at the

240 mg BID dose level: 1 DLT of Grade 3 tumor lysis syndrome and 1 DLT of Grade 3 thrombocytopenia.

As presented at World Conference on Lung Cancer 2018 and American Thyroid Association 2018, with a data cutoff of 19 July 2018, among the first 82 patients enrolled in LIBRETTO-001, the overall response rate (ORR) was 68% (95% confidence interval [CI] 50% to 82%, n=26/38) in *RET* fusion-positive NSCLC, 78% (95% CI 40% to 97%, n=7/9) in *RET* fusion-positive thyroid (nonmedullary thyroid cancer [MTC]), 50% (n=1/2) in *RET* fusion-positive pancreatic, 59% (95% CI 39% to 77%, n=17/29) in *RET*-mutant MTC, and 0% (n=0/4) in patients without a known activating *RET* alteration in their cancers (Drilon et al. 2018; Wirth et al. 2018). Responses did not differ by fusion partner, mutation (including the V804M gatekeeper resistance mutation), or prior therapies, including MKIs with anti-*RET* activity. Confirmed intracranial responses were achieved in 100% (n=5/5: 1 complete response, 4 partial responses) of patients with measurable brain metastases. The median duration of response was not reached. A total of 96% (49/51) of responding patients were still on treatment (median follow-up of responders - 8.8 months).

2.3. Benefit/Risk Assessment

The benefit-risk assessment for selpercatinib is considered in the context of the significant unmet medical need for patients with metastatic *RET*-fusion positive NSCLC who require systemic therapy. Patients who have driver alterations that can be matched with a targeted agent (e.g., erlotinib, osimertinib, crizotinib, alectinib) have demonstrated improved outcomes relative to patients who receive nonspecific therapy such as chemotherapy. Although patients with *RET*-fusion-positive NSCLC have an identifiable driver alteration, they currently receive the same SOC treatment as patients with NSCLC who do not have a driver alteration, as there are no *RET*-specific approved therapies. The magnitude and durability of the responses observed in *RET* fusion positive NSCLC patients in the Phase 1 study LIBRETTO-001 suggest that selpercatinib provides meaningful clinical efficacy. The benefits demonstrated with selpercatinib are consistent and meaningful across multiple endpoints, including among fusion partners.

The safety profile of selpercatinib is well-tolerated, clinically manageable, and distinct from available therapies, with the low rates of study drug discontinuation due to adverse events (AEs), particularly when compared to platinum-based SOC treatment regimens. As outlined in the IB, the most common toxicities associated with selpercatinib are monitorable and reversible and include dry mouth, diarrhea, hypertension, fatigue, constipation, AST/ALT elevation, headache, nausea, peripheral edema, and increased blood creatinine. The majority of events were Grade 1 or 2. Events of special interest include hypersensitivity, liver-function test abnormalities, thrombocytopenia, and hypertension.

Although the study procedures in Study JZJC are generally consistent with SOC, increased monitoring of vital signs (including blood pressure), hematology, hepatic panels, and ECGs occur in the initial cycles to monitor for potential toxicities of interest. Additionally, an Independent Data Monitoring Committee (IDMC) will assess unblinded safety data during the trial on a regular basis. The IDMC will evaluate all safety-related data provided for each meeting to determine whether a change in the conduct of the trial is warranted for the safety of patients.

Given the high unmet need for additional therapies to treat *RET* fusion-positive NSCLC, the clinical safety profile of selpercatinib, and the clinical efficacy observed in patients with *RET*-

altered solid tumors (including NSCLC) in the ongoing Phase 1/2 trial, the risk/benefit assessment supports evaluation of selpercatinib in the proposed patient population.

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated AEs of selpercatinib is to be found in the IB.

More detailed information about the known and expected benefits and risks of carboplatin, cisplatin, pemetrexed, and pembrolizumab may be found in the Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare PFS of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) therapy, pemetrexed, and pembrolizumab in patients with advanced or metastatic *RET* fusion-positive NSCLC • To compare PFS of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) and pemetrexed therapy, with or without pembrolizumab, in patients with advanced or metastatic *RET* fusion-positive NSCLC	• PFS per RECIST 1.1 by BICR
Secondary	
• To compare the efficacy of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) therapy, pemetrexed, and pembrolizumab in patients with advanced or metastatic *RET* fusion-positive NSCLC • To compare the efficacy of selpercatinib with the combination of platinum-based (carboplatin or cisplatin) and pemetrexed therapy, with or without pembrolizumab, in patients with advanced or metastatic *RET* fusion-positive NSCLC	• PFS per RECIST 1.1 by investigator • ORR/DOR/DCR per RECIST 1.1 by BICR • ORR/DOR/DCR per RECIST 1.1 by investigator • Intracranial ORR/DOR per RECIST 1.1 by BICR • Time to CNS progression per RECIST 1.1. by BICR • Intracranial ORR/DOR per RANO-BM by BICR • OS • PFS2 • Time to deterioration in pulmonary symptoms: cough, chest pain, and dyspnea as measured by the NSCLC-SAQ
• To assess safety and tolerability of selpercatinib compared to platinum-based and pemetrexed therapy with pembrolizumab • To assess safety and tolerability of selpercatinib compared to platinum-based and pemetrexed therapy with or without pembrolizumab	• Including but not limited to SAEs, AEs, deaths, and clinical laboratory abnormalities per CTCAE v5.0

• To assess/evaluate performance of *RET* local laboratory tests compared to a single central test	• *RET* fusion status
Tertiary/Exploratory	
• To compare patient-reported tolerability outcomes, including symptomatic adverse events and overall side-effect bother between patients treated with selpercatinib versus the combination of platinum-based (carboplatin or cisplatin) and pemetrexed therapy, with or without pembrolizumab	• Symptomatic Adverse Events: PRO-CTCAE • Overall Side-effect Bother (FACT-GP5)
• To compare patient-reported Physical Functioning and HRQoL between patients treated with selpercatinib versus the combination of platinum-based (carboplatin or cisplatin) and pemetrexed therapy, with or without pembrolizumab	• Physical Functioning: EORTC QLQ-C30 Physical Functioning Subscale (and EORTC IL19) • Other HRQoL Outcomes: EORTC QLQ-C30
• To compare *RET* fusion status in tumor and blood samples	• *RET* fusion status
• To assess the relationship between biomarkers and clinical outcomes	• Biomarkers assessed from blood or tissue samples, unless precluded by local regulations • Clinical outcomes data
• To assess efficacy of selpercatinib in patients randomly assigned to Arm B who crossed over to selpercatinib	• PFS/ORR/DOR/DCR after crossover
• To assess the pharmacokinetics of selpercatinib	• Predose plasma concentrations at Day 8 of Cycle 1, and at Day 1 of Cycles 2 through 6.

Abbreviations: AE = adverse event; BICR = blinded independent central review; CNS = central nervous system; CTCAE = Common Terminology Criteria in Adverse Events; DCR = disease control rate; DOR = duration of response; EORTC IL19 = European Organisation for Research and Treatment Item Library 19; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0.; FACT-GP5 = Functional Assessment of Cancer Therapy-Side Effects; HRQoL = health-related quality of life; NSCLC = non-small cell lung cancer; NSCLC-SAQ = Non-small Cell Lung Cancer Symptom Assessment Questionnaire; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; PRO-CTCAE = patient-reported outcome Common Terminology Criteria for Adverse Events; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

4. Study Design

4.1. Overall Design

This is a global, multicenter, randomized, open-label, controlled Phase 3 study comparing selpercatinib (Arm A) to platinum-based and pemetrexed therapy with or without pembrolizumab (Arm B) in patients with advanced or metastatic, *RET* fusion-positive nonsquamous NSCLC.

Patients will be stratified based on:

- geography (East Asia vs. non-East Asia),
- brain metastases per investigator assessment (presence vs. absence or unknown), and
- investigator's choice of treatment with or without pembrolizumab. This decision must be determined at the time of randomization.

Adult patients with histologically confirmed, unresectable, locally advanced or metastatic nonsquamous NSCLC with no previous systemic therapy for metastatic disease will be eligible.

Patients will be required to have a documented *RET* fusion in tumor and/or blood identified via NGS and/or PCR assays, as performed in the routine course of clinical care. Laboratories used for *RET* testing must have certification by Clinical Laboratory Improvement Amendments (CLIA), International Organization for Standardization/Independent Ethics Committee (ISO/IEC), College of American Pathologists (CAP), or other similar certification. After confirmation of eligibility, approximately 250 patients will be randomly assigned in a 2:1 ratio to:

- Arm A: treated with selpercatinib (160 mg BID continuously in 21-day cycles) or
- Arm B: treated with pemetrexed (500 mg/m^2 IV) every 3 weeks plus the investigator's discretion of the following treatments administered every 3 weeks:
    - 4 cycles of carboplatin (AUC 5, maximum dose 750 mg IV) or cisplatin (75 mg/m^2 IV)
    - with or without pembrolizumab (200 mg IV) up to 35 cycles

After the completion of 4 cycles of chemotherapy without progressive disease, patients randomly assigned to Arm B will receive maintenance therapy with pemetrexed (500 mg/m^2) with or without pembrolizumab (200 mg) every 3 weeks according to the decision made at the time of randomization. Patients with the intent by the investigator to be treated without pembrolizumab will be restricted to 20%. Treatment will continue until radiographic disease progression confirmed by BICR, unacceptable toxicity, withdrawal of consent, or death.

Patients randomly assigned to Arm B who discontinue treatment for radiographic disease progression that is confirmed by BICR may be eligible for crossover to selpercatinib (see Section 5.2.2). Crossover treatment will be optional at the discretion of the investigator.

The primary efficacy population is defined as all randomized patients with investigator's intent-to-treat (ITT) with pembrolizumab if randomized to Arm B (ITT-pembrolizumab population; defined in Section 9.3); patients will be analyzed according to assigned treatment group without regard to received treatment.

The primary endpoint of PFS per RECIST 1.1 by BICR in the ITT-pembrolizumab population will act as a gatekeeper for the endpoint of PFS by BICR in the ITT population, i.e., PFS in the ITT population will be tested conditionally on achieving statistical significance for PFS in the ITT-pembrolizumab population. The study will be considered to be a positive study if a statistically significant improvement in PFS by BICR in the ITT-pembrolizumab population is observed. Progression-free survival by BICR in the ITT population, in turn, will act as a gatekeeper for testing OS in the ITT population, i.e., the OS in ITT population will be tested conditionally on achieving statistical significance for the PFS in the ITT population. This ordering of the endpoint hierarchy is driven by the need to satisfy certain country-specific regulatory and payer expectations. Testing strategy of other secondary endpoints will be further described in the SAP.

4.2. Scientific Rationale for Study Design

This study is a head-to-head comparison of selpercatinib vs. a SOC for the treatment of advanced or metastatic nonsquamous NSCLC. The SOC arm consists of platinum-based therapy (cisplatin or carboplatin) with pemetrexed, with or without pembrolizumab. Patients with squamous NSCLC will be excluded to be consistent with the pemetrexed label. Although pembrolizumab in combination with platinum-based chemotherapy has been approved for patients with NSCLC in some geographies, it is not considered a global SOC. There are geographical differences in the frequency with which pembrolizumab is used based on individual patient characteristics that may influence the expected efficacy and safety (e.g., contraindications, PD-L1 expression, the potential for subsequent therapy with targeted agents whose toxicity profile may be affected by prior treatment with pembrolizumab). Additionally, not all patients are suitable to receive an immune checkpoint inhibitor such as pembrolizumab (e.g., patients with a history of interstitial lung disease (ILD) or interstitial pneumonitis, an active autoimmune disease, or requiring concurrent treatment with supraphysiologic doses of immunosuppressive agents). The design of Study JZJC, which allows the platinum doublet to be administered with or without pembrolizumab, provides flexibility for the investigator to select the regimen most well-suited for each specific patient. The preliminary results evaluating selpercatinib in *RET*-fusion-positive NSCLC have been previously described. Efficacy appears independent of line of therapy. Response rates and duration of therapy compare favorably to SOC therapies (Gandhi et al. 2018). Given these results, a comparative trial of selpercatinib vs. SOC appears justified.

The study will allow crossover of patients whose disease has progressed on chemotherapy with or without pembrolizumab. The preliminary results from a prior study in NSCLC suggest that selpercatinib will be effective in patients who have received prior treatment (Drilon et al. 2018; NCT03157128). The crossover design will therefore allow patients whose disease progresses on SOC therapy to receive selpercatinib.

4.3. Justification for Dose

Based on preclinical pharmacology experiments with human cancer cells in vitro and in murine xenograft models, meaningful inhibition of *RET* in tumors is expected to be achievable with oral dose regimens at total daily doses ≥40 mg/day. The dosage of 160 mg BID was selected as the recommended Phase 2 dose based on safety data (N=82) and preliminary efficacy data in

64 evaluable patients treated at doses from 20 mg QD through 240 mg BID (Drilon et al. 2018, NCT03157128). See the IB for additional information.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

5. Study Population

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

5.1. Inclusion Criteria

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

Type of Participant and Disease Characteristics

1. Histologically or cytologically confirmed Stage IIIB-IIIC or Stage IV NSCLC that is not suitable for radical surgery or radiation therapy (Amin et al. 2017). The histology of the tumor must be predominantly nonsquamous. Squamous cell and/or mixed small cell/non-small cell histology is not permitted.
2. Must have a *RET* gene fusion in tumor using PCR or NGS. Results in blood using NGS are also acceptable.
    - The *RET* gene fusion result should be generated from a laboratory with CLIA, ISO/IEC, CAP, or other similar certification that clearly denotes the presence of a *RET* alteration. Blood results must be determined on a platform that meets these standards and is also Lilly approved.
    - In all cases, the presence of the *RET* fusion must be confirmed upon review of the pathology report by Lilly or designee prior to enrollment.
3. Must have measurable disease per RECIST 1.1 (Eisenhauer et al. 2009) as assessed by the investigator. Target lesions situated in a previously irradiated area are considered measurable if progression has been determined in such lesions, and the location of previously irradiated lesions is clearly documented.
4. Must have Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2 (Oken et al. 1982).
5. Must have life expectancy of at least 3 months.
6. Must have adequate organ function, as defined subsequently. These values must be met during the baseline visit prior to randomization.

System	Laboratory Value
Hematologic	
ANC	≥1.5×10^9/L
Platelets	≥100×10^9/L
Hemoglobin	≥9 g/dL
Note: transfusions to increase a participant's hemoglobin level or initiation of erythropoietin or G-CSF therapy to meet enrollment criteria are not allowed in the 28 days preceding the first dose of study drug.	
Coagulation	
INR or PT	≤1.5X ULN unless the subject is receiving anticoagulation therapy
aPTT or PTT	≤1.5X ULN unless the subject is receiving anticoagulation therapy
Hepatic	
Total bilirubin	≤1.5X ULN Except participants with a documented history of Gilbert syndrome who must have a total bilirubin level of <3.0X ULN
	Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5X ULN
ALT and AST	<2.5X ULN **OR** ≤5X ULN if the liver has tumor involvement
Renal	
Measured creatinine clearance **OR**	≥50 mL/min
Calculated creatinine clearance (Appendix 7)	

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; dL = deciliter; G-CSF = granulocyte-colony-stimulating factor; g = gram; INR = international normalized ratio; L= liter; mL = milliliter; min = minute; PT = prothrombin time; PTT = partial thromboplastin time; ULN= upper limit of normal.

7. Ability to swallow capsules.

Contraception

8. Men with partners of childbearing potential or women of childbearing potential must agree to use a highly effective contraceptive method (e.g., intrauterine device or birth control pill) during treatment with study drug and for 6 months following the last dose of study drug. See Appendix 3. In addition, male subjects on selpercatinib should use a condom while on study treatment and males randomized to Arm B should use a condom while on study treatment and for 91 days following the last dose of pemetrexed.

Note: Unless not allowed by local regulations, women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

9. Women of childbearing potential must:
    - Have a negative pregnancy test (serum or urine, consistent with local regulations) documented within 24 hours prior to treatment with study drug.
    - Not be breast-feeding during treatment and for at least 4 months after the last dose of study drug.

Informed consent

10. The participant must be capable of demonstrating an understanding of the nature, significance, and implications of participation in the trial and giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Age

11. Are of an acceptable age to provide informed consent according to local regulations and are at least 18 years of age.

5.2. Exclusion Criteria

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

Medical Conditions

12. Have additional validated oncogenic drivers in NSCLC, if known: e.g., activating mutations of *EGFR*, *BRAF*, or *KRAS*, *MET* exon 14 mutations or high-level *MET* amplification or fusions of *ALK*, *ROS*, or *NTRK 1/2/3*.
13. Have symptomatic CNS) metastases, carcinomatous meningitis, or untreated spinal cord compression. Any previous definitive treatment or glucocorticoid therapy to treat CNS metastases must be completed at least 2 weeks prior to randomization and patients must be neurologically stable for 2 weeks prior to randomization.
14. Have clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of study treatment or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) >470 msec on more than 1 ECG obtained during the baseline period.

    Note: Patients with implanted pacemakers may enter study without meeting corrected QT interval (QTc) criteria due to nonevaluable measurement.

15. Have uncontrolled, disease-related, pericardial effusion or pleural effusion.

16. Have a history of human immunodeficiency virus ([HIV]; known HIV 1/2 antibodies positive). If the medical history, symptoms, and/or laboratory values suggest the patient may have HIV, appropriate assessments should be conducted to determine if the patient should be excluded.
17. Have known active Hepatitis B or C.
    - Patients with serological evidence of chronic hepatitis B virus (HBV) infection who have no known underlying liver cirrhosis (screening not required) and an HBV viral load below the limit of quantification with or without concurrent viral suppressive therapy (at a stable dose) are allowed. Patients with detectable HBV DNA and controlled disease may be permitted on therapy with sponsor approval. Concurrent viral suppressive therapy will be required for patients with detectable HBV DNA.
    - Patients with a history of hepatitis C virus (HCV) infection who have completed viral suppressive therapy and have a viral load below the limit of quantification are allowed.
    - If the medical history, symptoms, and/or laboratory values suggest that the patient may have active hepatitis B or C, appropriate assessment should be conducted to determine if the patient should be excluded.
18. Have active, uncontrolled, systemic bacterial, viral, or fungal infection that requires treatment or have serious ongoing intercurrent illness that is not controlled, despite optimal treatment (e.g., hypertension, diabetes, clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction, or peritoneal carcinomatosis). Screening for chronic conditions is not required.
19. Have clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug.
20. Other malignancy unless nonmelanoma skin cancer, carcinoma in situ of the cervix or other in situ cancers, or a malignancy diagnosed ≥2 years previously and not currently active. Patients receiving adjuvant hormone therapy for breast or prostate cancer with no evidence of disease are eligible.

Prior/Concomitant Therapy

21. Has had any of the following prior to randomization:
    - Prior systemic therapy (chemotherapy, immunotherapy, or biological therapy) for metastatic disease. Patients who received adjuvant or neoadjuvant therapy are eligible if the last dose of the systemic treatment was completed at least 6 months prior to randomization.
    - Major surgery (excluding placement of vascular access) within 3 weeks prior to planned start of study treatment.
    - Radiotherapy for palliation within 1 week of the first dose of study treatment or any radiotherapy within 6 months prior to the first dose of study treatment if more than 30 Gy to the lung.

- Any unresolved toxicities from prior therapy greater than Common Terminology Criteria in Adverse Events (CTCAE) Grade 1 at the time of starting study treatment except for alopecia and Grade 2, prior therapy related neuropathy.

22. Are taking a concomitant medication that is known to cause QTc prolongation (e.g., see Attachment 5).
23. Criteria #23 has been removed.
24. Criteria #24 has been removed.
25. Require chronic treatment with steroids. Intermittent use of inhaled steroids for asthma or local steroid injections is allowed. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of chronic treatment and does not need to be excluded. The use of topical, ophthalmic, inhaled, and intranasal corticosteroids is permitted. However, immunosuppressive therapy within 1 week prior to the first dose of study medication is not permitted.
26. Have received a live vaccine within 30 days prior to the first dose of trial treatment. Seasonal flu vaccines that do not contain live virus are permitted.
27. Are unable to interrupt nonsteroidal anti-inflammatory drugs (NSAIDs) 2 days before (5 days for long-acting NSAIDs), the day of, and 2 days following administration of pemetrexed.

Prior/Concurrent Clinical Study Experience

28. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
29. Have participated, within the past 30 days (4 months for studies conducted in Japan; 3 months for studies conducted in the UK), in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (4 months for studies conducted in Japan; 3 months for studies conducted in the UK [whichever is longer]) should have passed. Exceptions will be considered on a case-by-case basis by the Lilly clinical research physician (CRP)/clinical research scientist (CRS).

Other Exclusions

30. Have a known hypersensitivity to any of the excipients of selpercatinib, platinum-containing drugs, or pemetrexed.
31. Are unable or unwilling to take folic acid, dexamethasone, or vitamin B12 supplementation.

5.2.1. Exclusion Criteria for Participants on Pembrolizumab

The following exclusion criteria should apply only for participants on Arm B who the investigator plans on treating with pembrolizumab:

32. Have a history of ILD or interstitial pneumonitis, including clinically significant radiation pneumonitis.

33. Have active autoimmune disease or any illness or treatment that could compromise the immune system within the past 2 years, or a syndrome or condition that requires corticosteroids or immunosuppressive agents. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and does not need to be excluded.
34. Use of escalating or chronic supraphysiologic doses of corticosteroids or immunosuppressive agents (such as, exceeding 10 mg/day of prednisone or equivalent). Use of topical, ophthalmic, inhaled, and intranasal corticosteroids permitted.
35. Have previously received pembrolizumab or have a known hypersensitivity to any of the excipients of pembrolizumab.

5.2.2. Enrollment Criteria for Crossover Treatment

Patients who are randomly assigned to Arm B who discontinue treatment for radiographic disease progression that is confirmed by BICR may be eligible for crossover to selpercatinib if they meet the following criteria:

a) Have radiographic disease progression using RECIST 1.1 as assessed by BICR and stopped their initial treatment with platinum-based therapy and pemetrexed with or without pembrolizumab.
b) Are willing and able to provide written informed consent to crossover treatment.
c) Have adequate hematologic, hepatic, and renal function as defined within the inclusion and exclusion criteria for initial eligibility (Sections 5.1 and 5.2).
d) Have all toxicities attributed to platinum-based chemotherapy with or without pembrolizumab resolved to ≤Grade1 (CTCAE v5.0) or baseline, with the exception of alopecia, Grade 2 platinum therapy-related neuropathy, or controlled Grade 2 hypothyroidism or hypertension.
e) Have not received any other anticancer systemic therapy since platinum-based pemetrexed therapy with or without pembrolizumab.
f) Have an ECOG performance status of 0 to 2.

Patients are eligible to be considered for crossover if:

- they meet the criteria above and
- they can initiate treatment with selpercatinib within 42 days the time of BICR confirmed progression.

Exceptions may be made on a case-by-case basis following approval from the sponsor.

Patients that may crossover should **not**:

- complete V801 at the end of their initial treatment, but should enter V201 and V300 prior to starting selpercatinib (SoA [Section 1.3]). Visit 201 will allow for the collection of Arm B posttreatment safety information for patients that do not crossover to selpercatinib within 30 (+/-7 days) of the last dose of study treatment.
- initiate selpercatinib any earlier than 21 days after their last dose of study treatment.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number. The interval between rescreening should be ≥2 weeks. Each time rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not reconstitute rescreening.

6. Study Intervention

Study intervention is defined as any medicinal product(s) medical device(s) intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

	Arm A (selpercatinib)	**Arm B** (Investigator's discretion of carboplatin or cisplatin + pemetrexed ± pembrolizumab)			
Intervention	Selpercatinib	Carboplatin	Cisplatin	Pemetrexed	Pembrolizumab (investigator's choice)
Dose	160 mg	AUC 5 (maximum dose 750 mg)	75 mg/m^2	500 mg/m^2 (with vitamin supplementation)	200 mg
Schedule	BID continuously in 21-day cycles	Day 1 Q3W for 4 cycles	Day 1 Q3W for 4 cycles	Day 1 Q3W	Day 1 Q3W up to 35 cycles
Route	Oral	IV	IV	IV	IV
Authorized as defined by EU Clinical Trial Regulation	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Authorized and used according to EU authorization	Authorized and used according to EU authorization

Abbreviations: AUC = area under the concentration versus time curve; BID = twice a day; IV = intravenous; m = meter; mg = milligrams; Q3W = every 3 weeks.

6.1.1. Selection and Timing of Doses

A cycle is defined as an interval of 21 days. A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation.

The actual doses of cisplatin and pemetrexed to be administered will be determined by calculating the patient's body surface area (BSA) at the beginning of each cycle. Although it is acceptable to recalculate more frequently, if the patient's weight does not fluctuate by more than ±10% from the weight used to calculate the prior cycle or from baseline, the BSA will not need

to be recalculated. A ±10% variance in the calculated total dose will be allowed for ease of dose administration.

Arm A: Selpercatinib doses will be administered at approximately the same times on each day, and BID dosing will be separated by approximately 12 hours (a minimum of 6 hours between consecutive doses). See Section 6.5.1.1 and Appendix 5 for concomitant therapy considerations (including food and beverage intake). In all other instances not listed in Section 6.5.1.1, selpercatinib can be taken with or without food.

Participants randomized to selpercatinib treatment must keep a daily diary to record dosing compliance, which will also be assessed at clinic visits by means of a capsule count in the returned bottle(s). Late doses (i.e., 4 or more hours after scheduled time) should be noted in the diary. Doses that are late by more than 6 hours should be skipped and recorded in the dosing diary as missed. Vomiting after dosing should be noted in the diary, and a vomited dose should not be redosed or replaced.

Arm B: Patients will begin dosing with investigator's choice of carboplatin or cisplatin, pemetrexed, and pembrolizumab (if applicable) on C1D1. After the completion of 4 cycles of chemotherapy without progressive disease, patients randomly assigned to Arm B will receive maintenance therapy with pemetrexed and pembrolizumab (if applicable) every 3 weeks. Guidance for administration is provided below, but it is acceptable to administer pre- or post-medications and study drugs per local practice and/or labels.

Drug	Administration
Pembrolizumab	• Investigator's choice determined at the time of randomization. • If applicable, administered as IV infusion over approximately 30 min on Day 1 prior to pemetrexed and platinum. • It is recommended that any chemotherapy premedications not be administered until at least 30 minutes after the completion of the pembrolizumab infusion. • If applicable, pembrolizumab will be discontinued after completion of approximately 2 years of treatment (completion of 35 treatments with pembrolizumab).

Pemetrexed	• IV infusion over approximately 10 minutes on Day 1. Should occur at a minimum 30 minutes after pembrolizumab.
	• All patients must receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid as shown below or per local practice and/or labels.
	  • Folic acid supplementation: To reduce toxicity, patients treated with pemetrexed must be instructed to take a low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
	  • Vitamin B12 supplementation (1000 µg): Will be administered as an intramuscular injection *approximately* 1 to 2 weeks prior to the first dose of pemetrexed and repeated approximately every 9 weeks until 3 weeks after the last dose of study therapy.
	  • Dexamethasone prophylaxis (4 mg, orally BID – or equivalent): Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for reasons other than routine rash prophylaxis (e.g., antiemetic prophylaxis).

Cisplatin	• Administered as an IV infusion approximately 30 minutes after the pemetrexed infusion for the first 4 cycles. • Cisplatin therapy should be immediately preceded and followed by hydration procedures and administered according to local practice and labels. Similarly, antiemetic therapy should follow local guidelines and labels.
Carboplatin	• Administered as an IV infusion over 15 to 60 minutes (approximately 30 minutes) after pemetrexed for

	the first 4 cycles as per local practice and labels. • Doses should be calculated using the Calvert formula (Calvert et al. 1989) and should not exceed 750 mg. • Antiemetic therapy should follow local guidelines and labels.

Abbreviations: BID = twice a day; IV = intravenous; min = minutes.

6.1.2. Packaging and Labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation/Handling/Storage/Accountability

Please consider the following for study intervention preparation/handling/storage/accountability:

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received; any discrepancies are to be reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions prior to dispensing, with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.
5. Investigators should consult the study drug information provided in the Pharmacy Manual or the product label for the specific administration information (including warnings, precautions, contraindications, adverse reactions, and dose modifications).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. However, Lilly will not have unblinded access to aggregate data from the clinical database, to preserve the integrity of the trial. An IDMC will monitor aggregate safety during the course of the trial on a regular basis. Details will be specified in a separate IDMC charter.

To minimize investigator bias, PFS will be determined based on the assessment of a BICR (see Section 8.1.2). Patients on Arm B will be allowed to cross over to selpercatinib only after progression has been confirmed by the BICR. Details of the BICR will be described in a separate BICR charter.

Patients will be randomly assigned to 1 of 2 treatments arms, stratified based on geography (East Asia vs. non-East Asia), brain metastases per investigator assessment (presence vs. absence or unknown), and investigator's choice of treatment (with or without pembrolizumab).

6.4. Study Intervention Compliance

For participants randomly assigned to selpercatinib treatment, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules, and reviewing patient diaries. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A patient will be considered noncompliant if he or she takes <75% of the planned doses for assigned study drug in a cycle. A patient will also be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of study drug over the course of the patient's treatment.

Study intervention that is administered intravenously will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates

The Lilly CRP/CRS should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Concomitant Therapy

Except as indicated in Section 6.5.2, patients are not allowed to receive concomitant systemic anticancer agents (including herbal drugs known to have antitumor activity), drugs with immunosuppressant properties, or any other investigational agents not specified in this protocol. Any disease progression requiring other forms of specific antitumor therapy will necessitate early discontinuation from the study.

Chronic treatment (>7 days) with steroids is not permitted except to treat symptoms from an immune-related AE or brain metastases. Changes in steroid use or doses, especially in the context of steroids used to treat brain metastases, should be recorded on the eCRF to facilitate assessment of Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM). Intermittent use of inhaled steroids for asthma or local steroid injections is allowed. Similarly, the use of topical, ophthalmic, and intranasal corticosteroids is permitted. Similarly, limited use of systemic corticosteroids (≤7 days) is permitted where it is considered SOC (e.g., as premedication for contrast allergy or for chronic obstructive pulmonary disease exacerbation). Replacement doses of steroids (e.g., prednisone 10 mg daily) are permitted while on study.

The concurrent use of drugs known to prolong QTc is prohibited (Appendix 5). Drugs with a possible or conditional risk should be avoided if possible.

Live vaccines should not be administered while on study treatment or within 90 days after the last dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, H1N1 flu, rabies, bacillus Calmette-Guérin, and typhoid. Seasonal flu vaccines that do not contain live virus are permitted.

6.5.1.1. Concomitant Therapy Considerations for Arm A

Avoid concomitant use of a PPI, H2 receptor antagonists, or locally-acting antacids with selpercatinib. If concomitant use cannot be avoided:

- Take selpercatinib with food (at least 400 calories) when co-administered with a PPI
- Take selpercatinib 2 hours before or 10 hours after administration of an H2 receptor antagonist

- Take selpercatinib 2 hours before or 2 hours after administration of a locally-acting antacid

Concomitant use of selpercatinib with a strong or moderate CYP3A inhibitor increases selpercatinib plasma concentrations, which may increase the risk of selpercatinib adverse reactions, including QTc interval prolongation. Avoid concomitant use of strong and moderate CYP3A inhibitors with selpercatinib. If concomitant use of strong and moderate CYP3A inhibitors cannot be avoided, reduce the selpercatinib dosage and monitor the QT interval with ECGs more frequently.

Concomitant use of selpercatinib with a strong or moderate CYP3A inducer decreases selpercatinib plasma concentrations, which may reduce selpercatinib antitumor activity. Avoid coadministration of strong or moderate CYP3A inducers with selpercatinib.

Selpercatinib is a moderate CYP2C8 inhibitor and a weak CYP3A inhibitor. Concomitant use of selpercatinib with CYP2C8 and CYP3A substrates increases their plasma concentrations, which may increase the risk of adverse reactions related to these substrates. Avoid coadministration of selpercatinib with CYP2C8 and CYP3A substrates where minimal concentration changes may lead to increased adverse reactions. If coadministration cannot be avoided, follow recommendations for CYP2C8 and CYP3A substrates provided in their approved product labeling.

Please refer to the IB for additional details.

6.5.1.2.Concomitant Therapy Considerations for Arm B

Ibuprofen (up to 400 mg daily QD) can be administered with pemetrexed in patients with normal renal function (creatinine clearance [CrCl] >80 mL/min); caution should be used while administering ibuprofen concurrently with pemetrexed to patients with mild to moderate renal insufficiency (CrCl from 45 to 79 mL/min). Patients with mild to moderate renal insufficiency should avoid taking NSAIDs with short elimination half-lives for a period of 2 days before, the day of, and 2 days following administration of pemetrexed.

In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives, all patients taking these NSAIDs should interrupt dosing for at least 5 days before, the day of, and 2 days following pemetrexed administration. If concomitant administration of an NSAID is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal, and gastrointestinal toxicity.

6.5.2. Palliative Medicine and Supportive Care for Arm A and Arm B

Standard supportive medications may be used in accordance with institutional guidelines and investigator discretion. These may include:

- hematopoietic growth factors to treat neutropenia, anemia, or thrombocytopenia in accordance with American Society for Clinical Oncology (ASCO) or European Society for Medical Oncology (ESMO) guidelines.
- red blood cells and platelet transfusions.
- antiemetic, analgesic, and antidiarrheal medications.
- electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels.

- brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered SOC (e.g., as premedication for chemotherapeutic agents specified in the protocol, contrast allergy, short courses to treat asthma, chronic obstructive pulmonary disease). Replacement doses of steroids (e.g., prednisone 10 mg daily) are permitted while on study.
- thyroid replacement therapy for hypothyroidism.
- bisphosphonates, denosumab, and other medications for the treatment of osteoporosis, prevention of skeletal-related events from bone metastases, and/or hypoparathyroidism.

Continuation of medications that the patient has been on for the previous 28 days is allowed, provided they are not on the list of prohibited concomitant medications (refer to Appendix 5). Such therapy may include hormonal therapy for patients with prior:

- prostate cancer (e.g., gonadotropin-releasing hormone [GnRH] or luteinizing hormone-releasing hormone [LHRH] agonists) or
- breast cancer (e.g., GnRH/LHRH agonists, aromatase inhibitors, selective estrogen receptor modulators, or degraders)

Local treatment while receiving study treatment (e.g., palliative radiation therapy or surgery for bone metastases) is permitted with sponsor approval. If the lesion that is to be treated is a target lesion, the lesion will be censored at the time of treatment. However, the patient may be eligible to remain on study drug treatment provided there are other lesions that can be followed up for progression. Additionally, the patient must not be considered to be clinically or radiographically progressing. Patients should have recovered from the acute effects of radiation or surgery prior to restarting treatment. For patients on Arm A, sponsor recommends holding selpercatinib for approximately 5 half-lives (approximately 7 days) before and after radiation therapy or surgery.

Recent guidance has encouraged a re-evaluation of common eligibility criteria to make clinical trials more representative of real world populations and provide great accessibility to clinical trials, especially for rare populations (Kim et al. 2017; FDA 2019; Forde et al. 2020). As a result, the exclusion criterion for hepatitis B and C was updated with amendment b to allow patients who are positive for either HBsAg or Anti-HBc to be enrolled in certain circumstances as outlined in Criteria 17. It is recommended that patients who are positive for either HBsAg or Anti-HBc and have an HBV viral load below the limit of quantification have concurrent viral suppressive therapy. It is also recommended these patients undergo regular monitoring of HBsAg and HBV DNA and if HBV DNA becomes detectable, prophylactic anti-HBV treatment be initiated (if the patient is not currently on viral suppressive therapy). Concurrent viral suppressive therapy will be required for patients with detectable HBV DNA and regular monitoring of HBsAg and HBV DNA is recommended.

6.6. Dose Modification Guidelines for Arm A and Arm B

The following rules should guide dosing:

- Toxicity must resolve to Grade ≤1 or baseline prior to resuming the next cycle except AEs with no immediate medical consequence that can be controlled with adequate

treatment (e.g., pain, alopecia, neuropathy, fatigue, nausea, vomiting, diarrhea, Grade 2 hypothyroidism, dry mouth, or Grade 2 hypertension).

- Reduction of only 1 chemotherapy drug is appropriate if in the opinion of the investigator, the toxicity is clearly related to 1 drug. If the toxicity is deemed to be related to more than 1 drug, then the dose of each drug should be reduced. If a dose reduction of a chemotherapy drug is required, the dose may not be re-escalated. Patients on Arm A who have been dose reduced and who tolerate selpercatinib without toxicity for at least 1 cycle may be re-escalated. Please see Section 6.6.1. and the IB for guidance on specific AEs. If more than 2 dose reductions are required for any agent on Arm A or Arm B, that drug should be discontinued. If the investigator deems it in the best interest of patients, those on selpercatinib with clinical benefit who have had 2 dose reductions may be allowed to continue treatment with additional reductions (e.g., recurrent AST or ALT increase) with CRP/CRS approval.
- If toxicity is clearly attributed to 1 chemotherapy drug, that drug alone may be discontinued. If patients experience toxicity attributed to cisplatin or carboplatin, the respective agent should be discontinued. Switching between platinum agents is permitted. Patients treated with platinum-based and pemetrexed therapy with or without pembrolizumab may have platinum and/or pemetrexed discontinued and continue pembrolizumab alone. Similarly, pembrolizumab may be discontinued and chemotherapy continued, if appropriate.
    - **For patients in Arm A:** Selpercatinib may be withheld for up to 28 days from the last dose to allow time to recover from toxicity.
    - **For patients in Arm B:** Initiation of a dose of chemotherapy may be delayed for a maximum of 21 days (42 days from prior dose) to allow a patient sufficient time for recovery from study treatment-related toxicity (e.g., a delay of 21 days from the planned Day 1 of the cycle). Pembrolizumab may be delayed for up to 12 weeks.
    - **For patients in Arm A or Arm B:** In exceptional circumstances, a longer delay is permitted upon agreement between the investigator and the Lilly CRP/CRS.
- Cycles are 21 days in duration regardless of dose interruption unless the dose interruption includes D1 of the next cycle, in which case the next cycle will start with resumption of study drug.

Dose reductions should be made according to the following table. In addition, the dose can be delayed or adjusted at the investigator's discretion as clinically indicated.

Dose reduction for study interventions

	Arm A (selpercatinib)	**Arm B** (Investigator's discretion of carboplatin or cisplatin + pemetrexed ± pembrolizumab)			
Intervention	Selpercatinib	Carboplatin	Cisplatin	Pemetrexed	Pembrolizumab (investigator's choice)
Dose Level 0 (Starting Dose)	160 mg BID	AUC 5 Max dose = 750 mg	75 mg/m^2	500 mg/m^2	200 mg
Dose Level -1	120 mg BID	AUC 3.75 Max dose = 562.5 mg	56 mg/m^2	375 mg/m^2	Not permitted
Dose Level -2	80 mg BID	AUC 2.5 Max dose = 375 mg	38 mg/m^2	250 mg/m^2	Not permitted
Dose Level -3	40 mg BID[a]	Discontinue	Discontinue	Discontinue	Not permitted

Abbreviations: AE = adverse event; AUC = area under the concentration versus curve; BID = twice daily; LFT = liver function test; m = meter; mg = milligrams.

[a] For some AEs (e.g., hypersensitivity reactions and LFT increases), an alternative re-escalation strategy should be followed. Additional information is provided in Section 6.6.1 of this protocol as well as Section 6 of the selpercatinib IB, Summary of Data and Guidance for the Investigator.

6.6.1. Dose Modifications and Toxicity Management Guidelines for Arm A

A patient who experiences a clinically significant AE may have selpercatinib dosing withheld to evaluate the AE and to allow for recovery (to Grade 1 or baseline level). Upon recovery, the patient may restart therapy if it is considered in his/her best interest to continue therapy. Upon restarting, the patient may have the dose reduced by at least 1 dose level. Please see Section 8.2.1. for guidance on dose adjustments related to prolonged QTcF.

Dose Modifications for Selpercatinib Hypersensitivity

Please refer to the IB for the most current guidance on management of selpercatinib hypersensitivity reactions. Recommended actions are shown below.

If selpercatinib drug hypersensitivity is suspected, study drug should be withheld and treatment with steroids at 1 mg/kg prednisone (or equivalent) should be initiated. Upon resolution, selpercatinib may be resumed at a reduced dose of 40 mg BID while continuing steroids at the same dose. Note that this dose reduction does not require sponsor approval. Hypersensitivity has recurred in some patients, typically at 3 to 6 hours following drug administration. Follow the guidelines below if hypersensitivity recurs:

- Discontinue selpercatinib for recurrent clinically significant hypersensitivity
- After a minimum of 7 days and in the absence of clinically significant recurrent drug hypersensitivity, the dose of selpercatinib may be escalated sequentially to 80 mg BID, 120 mg BID, and 160 mg BID. Once the patient has tolerated treatment for a minimum of 7 days at the final dose, steroids may be tapered slowly.

Dose Modifications for Selpercatinib Liver Function Test Abnormalities

If a patient experiences ≥Grade 3 elevated liver function test (LFT) increases, study drug should be withheld and evaluation for potential alternative causes should be conducted (e.g., history of other hepatotoxic medications/substances, viral serologies, liver imaging). A repeat value 3 to 5 days after the initial finding of elevation of LFTs should be obtained to confirm the abnormality and to confirm if it is increasing or decreasing. Thereafter, LFTs should be monitored at least weekly until resolution to normal/baseline (depending on the clinical situation, resolution to Grade 1 if baseline is acceptable but waiting until normalization is preferable). If the LFT abnormalities do not begin to resolve (or worsen) within 5 days of the AE, a hepatology consultation should be considered to evaluate the need for a liver biopsy.

Upon resolution, for patients who received 160 mg BID or 120 mg BID, the selpercatinib dose should be reduced by 2 dose levels (80 mg BID or 40 mg BID, respectively) with weekly LFT monitoring. In the absence of recurrent LFT abnormalities, the dose of selpercatinib may be escalated sequentially to the next highest dose (120 mg BID or 80 mg BID, respectively) after a minimum of 2 weeks and again to the original dose and after a minimum of an additional cycle. Once the patient has been treated at a stable dose of selpercatinib for a minimum of 1 cycle without recurrent LFT abnormalities, the frequency of LFT monitoring may be decreased (e.g., midcycle for 2 cycles and then at the start of every cycle thereafter). For patients who experience ≥Grade 3 elevated LFTs at 80 mg BID, the sponsor should be contacted for additional guidance regarding dose modification. If the patient experiences ≥Grade 3 elevated LFTs at a dose of 40 mg BID, selpercatinib should be discontinued. Please refer to Section 8.2.2 for additional monitoring that may need to be initiated.

Dose Modifications for Thrombocytopenia

If a patient is discovered to have thrombocytopenia ≥Grade 3, study drug should be withheld and the patient should be evaluated for alternative causes (medications/substances, viral studies). A hematology consultation may be considered, as necessary, to understand the etiology and to consider a role for concomitant steroid therapy. The patient should undergo weekly complete blood count (CBC) testing until the event resolves and CBC level returns to normal/baseline. Upon recovery, the patient should resume selpercatinib with a dose reduction of at least 1 level with weekly CBC surveillance for 1 full cycle.

Dose Modifications for Hypertension

Hypertension is defined as:

- a sustained increase in blood pressure from baseline, as evidenced by ≥2 readings on ≥2 separate occasions, or
- a clinically significant elevation requiring acute treatment.

If hypertension occurs, study drug may be interrupted at the discretion of the investigator while:

- a new antihypertensive medication regimen is initiated, or
- a preexisting regimen is optimized to a reproducible reading of ≤140/90 mmHg.

If study drug is interrupted, it may be resumed at the same or a lower dose at the discretion of the investigator. In all cases, the patient should continue to undergo regular blood pressure monitoring to ensure adequate blood pressure control. Dose re-escalation to the patient's original dose can be considered once adequate BP control has been obtained; with clinically appropriate monitoring.

Dose Modification for Selpercatinib Interstitial Lung Disease/Pneumonitis

For Grade 2, withhold selpercatinib until resolution. Resume at next lower dose. Discontinue selpercatinib for recurrent ILD/pneumonitis.

For Grade 3 or 4, discontinue selpercatinib.

6.6.2. Dose Modification and Toxicity Management Guidelines for Arm B

6.6.2.1. Dose Modification for Chemotherapy

Please refer to the product label for the current dose modification and toxicity management guidelines for carboplatin, cisplatin, and pemetrexed. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. The following information provides recommendations for dose adjustments. These serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Recommended Dose Modifications for Chemotherapy: Hematological Toxicity

Platelets	ANC	Pemetrexed	Cisplatin/Carboplatin
		Dose Level (DL) from the **Dose reduction for study interventions** table	
≥50x 10^9/L AND	≥0.5 x 10^9/L	DL 0	DL 0
≥50 x 10^9/L AND	<0.5 x 10^9/L	DL -1	DL -1
<50 x 10^9/L without bleeding AND	ANY	DL -1	DL -1
<50 x 10^9/L with Grade ≥2 bleeding AND	ANY	DL -2	DL -2
ANY AND	neutropenic fever	DL -1	DL -1

Recommended Dose Modifications for Chemotherapy: Nonhematological Toxicity

Event	CTCAE Grade	Pemetrexed	Cisplatin	Carboplatin
		Dose Level (DL) from the **Dose reduction for study interventions** table		
Nausea or vomiting[a]	Grade 3 or 4	DL 0	DL 0	DL 0
Diarrhea	Grade 3 or 4	DL -1	DL -1	DL 0
Mucositis	Grade 3 or 4	DL -2	DL 0	DL 0
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3 or 4	DL -1	Discontinue	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other nonhematological toxicity[b]	Grade 3 or 4	DL -1	DL -1	DL -1

Abbreviations: CTCAE = Common Terminology Criteria in Adverse Events.

[a] Despite maximal treatment.

[b] Of medical consequence that cannot be controlled with treatment.

For patients who develop a clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) during initiation of pemetrexed therapy, consideration should be given to draining the effusion prior to dosing. However, if, in the investigator's opinion, the effusion represents progression of disease, the patient should be discontinued from study therapy.

No dosage adjustment is needed in patients with CrCl >45 mL/min. Insufficient numbers of patients have been studied with CrCl <45 mL/min to give a dose recommendation. Therefore, pemetrexed/platinum should not be administered to patients whose CrCl is <45 mL/min.

6.6.2.2. Dose Modification for Pembrolizumab

An immune-related adverse event (irAE) may be defined as an AE consistent with an immune-mediated chronic inflammatory reaction associated with drug exposure. These irAEs may occur shortly after the first dose or several months after the last dose of drug and may affect

more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment are critical to reduce complications. Based on existing clinical study data, most irAEs are reversible and can be managed with interruptions of therapy, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue therapy and administer corticosteroids. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. Dose modification and toxicity management guidelines for potential irAEs are provided in the following table.

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Institutional guidelines and applicable local recommendations should be followed for the management of pembrolizumab infusion reactions.

Please refer to the product label, ESMO guidelines (Haanen et al. 2017), ASCO guidelines (Brahmer et al. 2018), and local guidance for the current dose modification and toxicity management guidelines for pembrolizumab. The following information provides recommendations for dose adjustments. They serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Immune-Related Adverse Reactions	Severity	Treatment Modification
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grades 0 to 1.[a]
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue.
Colitis	Grade 2 or 3	Withhold until adverse reactions recover to Grades 0 to 1.[a]
	Grade 4 or recurrent Grade 3	Permanently discontinue.
Nephritis	Grade 2 with creatinine >1.5 to ≤3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grades 0 to 1.[a]
	Grade ≥3 with creatinine >3 times ULN	Permanently discontinue.
Endocrinopathies	Symptomatic hypophysitis Type 1 diabetes associated with Grade ≥3 hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or associated with ketoacidosis hyperthyroidism Grade ≥3	Withhold until adverse reactions recover to Grades 0 to 1.[a] For patients with Grade 3 or 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.

Immune-Related Adverse Reactions	Severity	Treatment Modification
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 to 5 times ULN or total bilirubin >1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0 to 1.[a]
	Grade ≥3 with AST or ALT >5 times ULN or total bilirubin >3 times ULN	Permanently discontinue.
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥50% and lasts ≥1 week	Permanently discontinue.
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grades 0 to 1.[a]
	Grade 4 or confirmed SJS or TEN	Permanently discontinue.
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0 to 1.[a]
	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barré syndrome	Permanently discontinue.
	Grade 4 or recurrent Grade 3	Permanently discontinue.
Infusion-related reactions	Grade 3 or 4	Permanently discontinue.

[a] If treatment-related toxicity does not resolve to Grade 0 to 1 within 12 weeks after the last dose of pembrolizumab, or if corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks, pembrolizumab should be permanently discontinued.

Pembrolizumab should be permanently discontinued for Grade 4 or recurrent Grade 3 adverse reactions, unless otherwise specified in the table above or as outlined per local guidelines and regulations.

6.7. Intervention after the End of the Study

The end of study is defined in Section 4.4. Investigators will continue to follow the SoA provided in Section 1.3 until notified by Lilly that the end of the study has occurred.

6.7.1. Treatment after Study Completion

Study completion occurs after the clinical trial database is locked and final analysis of primary and secondary endpoints has been performed. Investigators will continue to follow SoA (Section 1.3) for all patients until notified by Lilly that study completion has occurred.

6.7.2. Continued Access

Participants who are still on study intervention at the time of study completion may continue to receive study intervention if they are experiencing clinical benefit and no undue risks.

The continued access period will apply to this study only if at least 1 participant is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access period begins.

Participants are not required to sign a new ICF before treatment is provided during the continued access period; the initial ICF for this study includes continued access under this protocol.

The participant's continued access to study intervention will end when a criterion for discontinuation is met (Section 7). Continued access follow-up will begin when the participant and the investigator agree to discontinue study intervention and lasts approximately 30 days. Follow-up procedures will be performed as shown in the Continued Access SoA.

Participants who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Crossover and long-term follow-up do not apply.

Participants who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent unless he or she has explicitly provided permission and consent.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Possible reasons leading to permanent discontinuation of investigational product:

- The participant or the participant's designee, e.g., legal guardian requests to discontinue investigational product.
- A clinically significant finding is identified (e.g., a change from baseline in QT interval or LFT abnormality) after enrollment. In such cases, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is warranted.

In addition, participants will be discontinued from using the investigational product under the following circumstances:

- The patient becomes pregnant during the study
- The patient is significantly noncompliant with study procedures and/or treatment
- Disease progression (radiographic or clinical progression). Exceptions for continuing study treatment beyond BICR-confirmed radiographic progression may be made on a case-by-case basis for patients who are believed to be clinically benefiting from study treatment, and the investigator and Lilly CRP/CRS agree that continuing study treatment is in the patient's best interest
- Unacceptable toxicity
- The patient, for any reason, requires treatment from another therapeutic agent that has been demonstrated to be effective for treatment of the study indication (except as noted in Section 6.5.2). Discontinuation from study treatment will occur prior to introduction of the new agent. If medically appropriate, the short-term follow-up procedures should also be completed prior to introduction of the new agent (even if the interval is less than 30 days from the last dose of study treatment)
- The investigator decides that the patient should be discontinued from study intervention

Participants discontinuing from using the investigational product for any reason should complete AE per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued under the following circumstances:

- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Patient's decision

- The patient or the patient's designee requests to be withdrawn from the study

Participants discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

7.2.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from using the study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment.

If the investigator and the sponsor CRP/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product.

Safety follow-up is as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

For sites located in the United Kingdom (UK) and Germany, refer to Appendix 6 for country-specific discontinuation guidelines.

7.3. 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. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

Discontinuation of specific sites or of the study as a whole is described in Section 10.1.8.2.

8. Study Assessments and Procedures

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards:

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed by the appropriate site personnel to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count, scans, *RET* testing) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

8.1.1. Imaging

To evaluate PFS, tumor assessments will be performed for each patient at the times shown in the SoA (Section 1.3) or whenever clinically indicated. Radiologic assessments obtained previously as part of routine clinical care and obtained prior to consent may be used as baseline assessment, provided they are of diagnostic quality and were done no more than 28 days before the first dose of study drug.

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, magnetic resonance imaging (MRI) is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast is strongly recommended unless not feasible/medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST 1.1 (Eisenhauer et al. 2009).

The method of tumor assessment used at baseline must be used consistently throughout the study. Radiologic scan of the thorax, abdomen, and pelvis is required, as well as any other areas

with suspected disease involvement. A baseline intracranial evaluation with CT or MRI is required for all patients. A bone scintigraphy (preferred) or PET scan or PET component of PET/CT scan should be obtained for patients with known nonmeasurable bone lesions. Note that RECIST 1.1 emphasizes bone scintigraphy is not adequate to measure bone lesions; however, bone scintigraphy can be used to confirm the presence or disappearance of bone lesions. Please see the Site Imaging Manual for guidelines on how the various imaging studies should be performed and transmitted for central review. It is recommended to confirm presence of malignant cells before determining progressive disease on imaging alone. Some patients receiving selpercatinib have been reported to have effusions and/or ascites which have subsequently been found to be chylous in nature (See Section 8.2.2.2 and IB for additional details).

Progression-free survival after next line of treatment (PFS2) will also be assessed. For patients who cross over to selpercatinib, tumor assessments will be performed for each patient at the times shown in the SoA (Section 1.3, Optional Crossover Treatment). For patients who do not cross over to selpercatinib, it is recommended that, to the extent it is feasible, the scan interval of approximately every 6 weeks for the first 2 assessments and then every 9 weeks for the next 48 weeks and then every 12 weeks thereafter is maintained during the subsequent line of therapy to adequately characterize PFS2.

8.1.2. BICR Assessment

Response assessments, including verification of partial response (PR) or complete response (CR) and disease progression, will be assessed by the BICR. These data will constitute the primary assessment for PFS and ORR analyses. The BICR will conduct 2 assessments of tumor response using RECIST 1.1: 1 for the overall systemic disease (based on target/nontarget and new lesions) and 1 solely for the evaluation of CNS endpoints (based on brain metastases only). The BICR will also conduct 1 assessment using RANO-BM (Lin et al. 2015) for the evaluation of CNS-related endpoints.

Following each scan in the main study, the investigator will assess for progression using RECIST 1.1 and submit the scan for BICR review as outlined in Section 1.3. It is anticipated that the BICR assessment to confirm progression will be completed prior to the next scheduled scan. In the rare cases where this is not the case, the patient should continue on the scan schedule until the BICR assessment is provided to the site. The following table outlines the potential actions following BICR review.

Investigator assessment	BICR assessment	Actions
Progressive Disease[a]	Progression verified	• Discontinue study treatment OR • Continue therapy with sponsor approval and signing of post-progression consent if the patient is believed to be clinically benefiting OR • Crossover (only patients progressing on Arm B are eligible for crossover) OR • Continue treatment per iRECIST (only for patients in Arm B receiving pembrolizumab)
	Progression not verified	• Continue on study treatment if the patient is

Investigator assessment	BICR assessment	Actions
		believed to be clinically benefiting (sponsor approval is not necessary) until a criterion for discontinuation is met **OR** • Discontinue study treatment; imaging should continue until (1) radiographic disease is verified by the BICR, (2) the start of a new anticancer therapy, (3) death, (4) withdrawal of consent, or (5) study completion. Note that these patients would be eligible to cross over upon BICR documentation of progression.
Nonprogression	In the case of investigator-assessed nonprogression, results are not reported back to investigator as BICR assessment is only used for endpoint assessment	• Continue on study treatment until progressive disease or another criterion for discontinuation is met

Abbreviations: BICR = blinded independent central review; iRECIST = immune Response Evaluation Criteria in Solid Tumors; PD = progressive disease.

[a] For patients where the investigator assessment is PD, it is at the discretion of the investigator if treatment is continued until the BICR assessment is received.

In the crossover period, scans will be collected and stored for future review, if needed. However, the BICR does not provide progression confirmation in the crossover period and progression is determined solely on investigator assessment.

For patients in Arm B who are receiving pembrolizumab, treatment decisions should be made using investigator-assessed immune Response Evaluation Criteria in Solid Tumors (iRECIST) (RECIST 1.1 for Immune-based Therapeutics; Seymour et al. 2017). For patients who have initial evidence of radiological progressive disease (PD) using RECIST 1.1 (i.e., unconfirmed PD by iRECIST), it is at the discretion of the investigator whether to continue a patient on study treatment until repeat imaging is obtained (using iRECIST for patient management). Study treatment may continue until criteria for confirmed PD are met (Seymour et al. 2017).

8.2. Safety Assessments

8.2.1. Electrocardiograms

Electrocardiogram monitoring should be performed as outlined in the SoA (Section 1.3). QTcF values should be recorded on the case report form (CRF). The following actions should be taken if the QTcF is greater than 500 msec on at least 2 of 3 ECGs and the triplicate average QTcF is greater than 500 msec or >60 msec longer than baseline:

- Manually review to confirm accuracy. Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site for immediate patient management.
- Assess for alternative causes (concomitant medications, electrolyte abnormalities, presence of pacemaker). Potassium should be ≥4 mEq/L and less than upper limit of normal (ULN) and magnesium and calcium should be within normal limits. If a potential

alternative cause is identified, the sponsor should be consulted for dose reduction guidance.
- Institutional guidelines or SOC measures for management of QTcF interval >500 msec and/or associated arrhythmias should be initiated.
- Clinical chemistry should be assessed and if electrolytes are abnormal, they should be repleted as indicated.
- If the patient is on Arm A, selpercatinib should be reduced at least 1 dose level.
- If the patient is on Arm B, dose adjustments should occur per label/institutional guidelines.

If a patient experiences QTcF >500 msec as defined earlier despite 2 dose reductions and if the investigator deems it in the best interest of the patient, he/she may continue treatment with study drug with CRP/CRS approval. In addition, Lilly may request copies of the ECGs for adjudication).

8.2.2. Clinical Safety Laboratory Assessments

- Blood will be collected so that Lilly may analyze safety laboratory values using a central vendor. Lilly or its designee will provide the investigator with the results of safety laboratory tests analyzed by a central vendor.
  - See Appendix 2 for the list of clinical laboratory tests to be performed and Section 1.3 (SoA) for the timing and frequency.
  - The investigator should review any clinically significant abnormal laboratory findings, and assess relevance to patient care. If the laboratory findings are clinically significant, the investigator should document the findings as an AE in the CRF (if not previously documented using local laboratories). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are based on investigator's judgment.
- In addition, investigator sites may use local laboratories to determine patient eligibility and treatment decisions.
- Regardless of whether or not central or local laboratory tests are used to determine patient care decisions, all laboratory tests with values considered clinically significantly abnormal during participation in the study or until completion of V801 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
  - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.2.2.1. Hepatic Safety Monitoring

In Study Participants with Baseline ALT/AST <1.5X ULN

If a study participant enrolled with baseline ALT/AST <1.5X ULN experiences elevated ALT/AST ≥3X ULN and elevated total bilirubin (TBL) ≥2X ULN, or ALT/AST≥5X ULN, liver testing (Appendix 4) including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the study CRP/CRS. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels.

In Study Participants with Baseline ALT/AST ≥1.5X ULN

If a study participant enrolled with baseline ALT/AST ≥1.5X ULN experiences elevated ALT/AST≥ 3X baseline or ALT/AST ≥2X baseline and TBL ≥2X ULN, liver testing (Appendix 4) including ALT, AST, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the study CRP/CRS. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels.

8.2.2.1.1. Special Hepatic Safety Data Collection

Hepatic data (Appendix 4) should be collected in the event that 1 (or more) of the following conditions is met for the patient during the course of the study:

- Patients enrolled with baseline ALT/AST <1.5X ULN:
    a. elevated ALT/AST ≥3X ULN and elevated TBL ≥2X ULN
    b. ALT/AST ≥5X ULN on 2 consecutive tests
- Patients enrolled with baseline ALT/AST ≥1.5X ULN (regardless of whether or not they have hepatic metastasis):
    a. elevated ALT/AST ≥2X baseline and elevated TBL ≥2X ULN
    b. elevated ALT/AST ≥3X baseline on 2 consecutive tests
- All patients:
    a. discontinuation from study treatment due to a hepatic event or abnormality of liver tests
    b. occurrence of a hepatic event considered to be an SAE

8.2.2.2. Chylothorax and Chylous Ascites Monitoring

If a patient develops a pleural effusion or abdominal ascites or both while on selpercatinib, fluid sampling and testing should be considered as part of the management algorithm whenever possible. The etiology of this finding varies and distinguishing chylous fluid from malignant (as

well as other causes such as infectious) may impact management significantly (for example, presumption of disease progression with premature discontinuation of therapy). Additionally, a diagnosis of chylous effusions or ascites or both may indicate a role for conservative measures such as fluid replacement, dietary alteration or medical therapy or both (for example, somatostatin analogue) prior to consideration of more invasive measures. Selpercatinib interruption and dose modification should follow the general strategy as outlined in Section 6.6 (Dose Modification), based upon severity and causality of the event.

8.2.2.3. Renal Safety Monitoring

In vitro, selpercatinib is an inhibitor of the drug transporter MATE1 and may reduce the clearance of MATE1 substrates (for example, creatinine). Selpercatinib may increase serum creatinine due to inhibition of the renal tubular secretion transporter MATE1, without affecting glomerular function. Complementary markers such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired

8.2.2.4. Thyroid Function Monitoring

Hypothyroidism was reported in patients receiving selpercatinib in clinical trials. Monitor patients for hypothyroidism and treat as medically appropriate. Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with preexisting hypothyroidism should be treated as per standard medical practice prior to the start of selpercatinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction during selpercatinib treatment. Thyroid function should be monitored periodically throughout treatment with selpercatinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice. However, patients could have an insufficient response to substitution with levothyroxine (T4), as selpercatinib may inhibit the conversion of levothyroxine to liothyronine (T3) and supplementation with liothyronine may be needed.

8.3. Adverse Events and Serious Adverse Events

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant. The investigator is responsible for the appropriate medical care of participants during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed up until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator. Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via CRF the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of

the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. The investigator should provide AE verbatim terms and then the terms will be mapped by Lilly or its designee to corresponding terminology within the Medical Directory for Regulatory Activities lower level term dictionary. The investigator will use CTCAE v5.0 to assign AE severity grades.

Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product, via CRF. The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment, or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, and/or study procedure and the AE. The investigator answers yes/no when making this assessment.

Disease progression of the primary tumor in and of itself is captured as an efficacy assessment and should not be captured as an AE (including fatal AEs) unless the disease progression is assessed as related to study treatment. If a new primary malignancy appears, it will also be considered an AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

Adverse events

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product or investigational combination product.
- An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational device.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, 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 intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. 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 AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

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

Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to

receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 8.3.1) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the CRF (see Section 8.2.2).

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to Lilly begins after the patient has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the AE CRF, not the Medical History CRF.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of investigator awareness. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available. Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.2. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 1.3).

8.3.3. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.4. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the completion of V801 or 120 days following the last dose of pembrolizumab.
- 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 Appendix 3.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 3.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8.3.5. Cardiovascular and Death Events

No additional reporting is required.

8.3.6. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

8.4. Treatment of Overdose

Refer to the IB and/or product label for selpercatinib, cisplatin, carboplatin, pemetrexed, and pembrolizumab for available information on the signs, symptoms, and treatment of overdose.

8.5. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of selpercatinib in Arm A only.

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling and prior dose will be recorded.

Blood for PK assessment will be collected on C1D8, and at the first day of each consecutive cycle up to Cycle 6. Samples are to be drawn within 2 hours prior to dose, and exact time of sample collection should be recorded. In addition, time of previous dose should be recorded. Additional PK may also be assessed in patients when considered necessary by the investigator to understand exposure in relationship to possible safety.

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for a maximum of 2 years following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism, transport and/or protein binding work.

8.6. Pharmacodynamics

Not applicable

8.7. Genetics

8.7.1. Whole Blood Sample for Pharmacogenetic Research

A blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples may be used to investigate variable response to selpercatinib, to investigate genetic variants thought to play a role in NSCLC and to determine whether genetic alterations identified in tumor samples are somatic or germline variants. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/IRBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of selpercatinib or after selpercatinib becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome and exome sequencing, genome-wide association studies, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

8.8. Biomarkers

8.8.1. Samples for Retrospective Evaluation of RET Status

If available, an unstained, archived tumor tissue sample in a sufficient quantity to allow for retrospective central analysis of *RET* fusion status should be provided as outlined in the Schedule of Activities:

a) Tumor samples must be formalin fixed and paraffin embedded (FFPE). Blocks should be provided wherever possible, but unstained slides are also permitted. Acceptable sample collection methods include, but are not limited to, surgical resection (preferred), core biopsy, endobronchial ultrasound bronchoscopy procedure (EBUS), or FFPE fine needle aspiration (FNA). Cell blocks or cytology samples in FFPE are acceptable. Biopsy samples taken from bone metastasis are unsuitable for testing and are not acceptable. Samples may be collected from primary or metastatic tumor sites.
b) The investigator site will be asked to provide at least 1 of the following, if available:
    a. FFPE tumor tissue blocks, or
    b. Preferably, at least 11 unstained FFPE slides. However, it is strongly recommended that 20 FFPE slides be submitted. Preferably, each section should be approximately 5 µm thick.

If it is considered safe to perform, patients who do not have sufficient available tumor tissue may undergo a fresh tumor biopsy/FNA.

Patients must have *RET* gene fusion as outlined in Section 5.1. For all patients, a redacted molecular pathology report or other report(s) describing tumor *RET* (and other) fusion analysis should be submitted to the sponsor, designee, and central laboratory to confirm trial eligibility. In regions or sites where *RET* testing is not SOC and/or an acceptable local test (as defined by Lilly) is not available, a prescreening consent will be used to provide information to the patient regarding testing to determine tumor *RET* status. The results of the initial or retrospective evaluation will include other genes. These genes include, but are not limited to, EGFR, ALK, ROS1, KRAS, BRAF, HER2, MET, NTRK1, NTRK2, or NTRK3.

8.8.2. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, resistance mechanisms, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including but not limited to deoxyribonucleic acid (DNA), cell free DNA, RNA, proteins, lipids, and other cellular elements.

Blood and tissue samples for biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow. Whole blood will be collected to compare *RET* fusion status in tumor and cfDNA samples. It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include pathology reports and data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 8.7 and 8.8.

Samples will be used for research on the drug target, disease process, variable response to selpercatinib, pathways associated with NSCLC and the mechanism of action of selpercatinib. These samples may also be used to develop related research methods or to validate diagnostic tools or assays.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigator site personnel.

An optional tissue biopsy may be collected at the time of progression (either on initial therapy and/or crossover) if it can be safely performed.

Lilly has a right to retain a portion of the submitted tissue. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned. For biopsies performed in the setting of disease progression, the sponsor should be contacted to inform them of the planned biopsy.

Samples will be retained at a facility selected by Lilly for a maximum 15 years after the last participant visit for the study, or for a shorter period if local regulations and IRB/ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of selpercatinib or after selpercatinib becomes commercially available. Technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, multiplex assays, whole genome sequencing, whole exome sequencing, RNA sequencing, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

8.9. Medical Resource Utilization and Health Economics

8.9.1. Patient-Reported Outcomes and Health Care Resource Utilization

Patient-reported questionnaires will be administered electronically according to the SoA (Section 1.3) in countries where the questionnaires have been translated into the native language of the region and linguistically validated. Patients that are illiterate or have religious restrictions

are not required to complete the questionnaires. The patient-reported outcomes will be used to compare pulmonary symptoms (NSCLC-Symptom Assessment Questionnaire [SAQ]) between treatment arms.

While individual patients may vary in their response time, it is estimated that 20 items (similar to this study) can be completed in an average of less than 4 minutes using an electronic device. Two recent publications have evaluated survey completion times. Of note, the number of items in this study are significantly lower than those studied. In this study, 67 items were completed in an average of 15 minutes, and 100% of patients reported the completion time as "about right" and 79% were willing to answer more questions (Girgis et al. 2017). The current study will apply much fewer items than investigated in these studies.

NSCLC-SAQ

This instrument measures overall severity of cough, pain, dyspnea, fatigue, and appetite (McCarrier et al. 2016). An electronic-based delivery method will be used in this study. The 7-day recall period requires weekly assessment by the patient via the provided device. Sites will not administer this instrument.

PRO-CTCAE

These items have been developed to assess select symptomatic AEs from the patient perspective associated with cancer therapy, to complement the CTCAE data collected at the site level (Basch et al. 2014; Bennet et al. 2016).

The reported outcome-CTCAE will be administered electronically directly to the patient via the electronic device provided on a weekly basis. Sites will not administer this instrument.

FACT-GP5

This is a single item from the Functional Assessment of Cancer Therapy-Side Effects general scale to assess the overall burden of the items reported via the PRO-CTCAE. This item will be administered electronically directly to the patient via the electronic device provided on a weekly basis. Sites will not administer this instrument.

EORTC QLQ-C30 and EORTC IL19

Health-related quality of life will be assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 (EORTC QLQ-C30; Aaronson et al. 1993).

The EORTC QLQ-C30 self-reported general cancer instrument consists of 30 items covered by 1 of 3 dimensions:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

Electronic versions of the questionnaires will be used and will be available to the patient on the provided electronic device. The full scale will be completed electronically on Day 1 of each cycle at the clinic site prior to receiving study treatment.

Note: The EORTC QLQ-C30 Physical Functioning score (items 1-5) will also be completed weekly by the patient using the device provided (not at the clinic site). In these instances, the physical functioning scale is referred to as the EORTC IL19 in order to comply with copyright requirements.

EQ-5D-5L

Health status will be assessed using the EuroQol Five Dimension Five Level questionnaire (EQ-5D-5L) (Janssen et al. 2008). These utility measures are an important input for economic evaluations concerning the value of treatment interventions. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the SoA. A unique EQ-5D health state is defined by combining 1 level from each of the 5 dimensions. Additionally, patients will indicate their current health status by marking on a visual analog scale ranging from 100 (best imaginable health state) to 0 (worst imaginable health state). The recall period is "today". The EQ-5D-5L is designed for self-completion by respondents and is cognitively simple, taking only a few minutes to complete, and will be administered electronically at the study site on Day 1 of each cycle prior to receiving study treatment. EQ-5D-5L responses may be incorporated into cost utility analyses, but will not be included in the clinical study report (CSR).

Health Care Resource Utilization

Health care resource utilization will be collected in the CRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected will include:

- hospitalization (yes or no) and duration of hospitalization (admission and discharge dates)
- emergency room visits (yes and number of events, or no)
- supportive care medications (granulocyte-colony-stimulating factor [G-CSF] use, analgesics, transfusions)

9. Statistical Considerations

9.1. Statistical Hypotheses

Treatment of patients with advanced or metastatic *RET* fusion-positive nonsquamous NSCLC with selpercatinib in the first-line setting will provide a clinically meaningful increase in PFS over treatment with platinum-based chemotherapy and pemetrexed in combination with or without pembrolizumab.

9.2. Sample Size Determination

The primary efficacy endpoints are progression-free survival (PFS) per BICR in the ITT-pembrolizumab and in the ITT population (defined in Section 9.3) with hypothesis testing conducted via the stratified log-rank test. Approximately 250 patients will be randomized at a ratio of 2:1 to selpercatinib versus control. The percentage of patients with the intent not to receive pembrolizumab (by investigator's choice) will be capped at 20% of the ITT population. As a result, a minimum of 200 patients will be enrolled in the ITT-pembrolizumab population. Under an alternative hazard ratio (HR) assumption of 0.563 (and the interim analysis plan specified in Section 9.5), a total of 140 PFS events in the ITT-pembrolizumab population are required to yield 89% overall statistical power at a 1-sided type I error rate of 0.025. If a mPFS of 9 months is assumed for patients in the Arm B (Gandhi et al. 2018), with exponentially distributed PFS, the hazard ratio assumption of 0.563 would correspond to an increase in mPFS of approximately 7 months associated with selpercatinib treatment (9 vs. 16 months with control vs. selpercatinib, respectively). Observation of the requisite PFS events in the ITT-pembrolizumab population will trigger the interim and final analyses of BICR PFS.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All participants who sign informed consent
Intention to treat (ITT)/Enrolled	All randomized patients, even if a patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Patients will be analyzed according to the treatment group they were assigned to regardless of what actual treatment they receive.
ITT-pembrolizumab	All randomized patients with investigator's intent to treat with pembrolizumab if randomized to control arm. Patients will be analyzed according to the treatment group they were assigned to regardless of what actual treatment they receive.
Evaluable	Defined in the following specific subsections if applicable.
Safety	All randomized patients who take at least 1 dose (including a partial dose) of study treatment. Analysis of safety data will be based on the actual treatment a patient received on the first study treatment administration regardless of which treatment they were randomized to receive ("as treated").

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated.

Continuous variables will be summarized using descriptive statistics (i.e., number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Handling of missing, unused, and/or spurious data is addressed prospectively in the overall statistical methods described in the protocol and/or SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

A detailed description of participant disposition will be provided according to the CONSORT publishing requirements.

9.4.2.2. Participant Characteristics

Patient demographic and baseline characteristics will be summarized. Baseline disease characteristics, prior anticancer therapies, historical illness, and preexisting conditions will also be summarized.

9.4.2.3. Concomitant Therapy

A summary of preferred names of concomitant medication by treatment arm by decreasing frequency will be generated.

9.4.2.4. Treatment Compliance: Selpercatinib Treatment Only

Applicable for patients randomly assigned to selpercatinib treatment only (Arm A). Compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. Study treatment taken will be derived from the difference between the total number of capsules dispensed and returned over the course of the patient's treatment. A patient will be considered noncompliant if he or she takes <75% or ≥125% of the planned doses.

9.4.2.5. Extent of Exposure

The duration on therapy, dose omissions, dose reductions, dose delays, and dose intensity for each drug will be summarized for all treated patients by arms.

9.4.2.6. Post-Study Treatment Therapy

The numbers and percentages of patients receiving poststudy anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), by drug class and/or name, overall, and by line of therapy.

9.4.3. Efficacy Analyses

All efficacy analyses will be performed using the ITT-pembrolizumab population and the ITT population, unless otherwise specified.

9.4.3.1. Primary Analysis

The primary endpoints are BICR PFS in the ITT-pembrolizumab population and BICR PFS in the ITT population. BICR PFS is defined as the time from randomization until the occurrence of documented disease progression by the BICR, per RECIST 1.1 criteria, or death from any cause in the absence of BICR-documented progressive disease. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment (a detailed PFS event/censoring scheme will be provided in the statistical analysis plan [SAP]). The BICR-PFS will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata (interactive web-response system data). The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by randomization strata. The PFS survival curves, mPFS, and PFS rates at various time points with 95% CI for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for PFS will be described in the SAP.

The analysis of BICR PFS is event driven. The interim PFS analysis will be conducted when approximately 93 events have been observed in the ITT-pembrolizumab population. Details are provided in Section 9.5. Approximately 140 BICR PFS events in the ITT-pembrolizumab population will trigger the final PFS analysis. Conditional on achieving statistical significance for the BICR PFS, the other primary endpoint, BICR PFS in the ITT population will be tested at interim and final analysis. To preserve the overall type I error rate at the 1-sided significance level of 0.025, O'Brien-Fleming boundaries will be used. A detailed alpha spending scheme will be provided in the statistical analysis plan. The study will be considered to be a positive study if PFS by BICR in the ITT-pembrolizumab population achieves the critical boundaries at interim or final analysis.

9.4.3.2. Key Secondary Analysis

Overall survival in ITT population is an error-controlled, key secondary endpoint. Overall survival is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. Overall survival will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata. The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified

by the randomization strata. Overall survival curves, the median and survival rates at various time points with 95% CI, for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958). Sensitivity analyses for OS will be described in the SAP.

Conditional on achieving statistical significance for both of the primary endpoints of BICR PFS in the ITT-Pembrolizumab and ITT populations, OS in the ITT population will be tested at the interim analysis, the final BICR PFS analysis or a separate final OS analysis. The final OS analysis (if needed) will be triggered upon observation of approximately 175 deaths, allowing a censoring rate of approximately 30% given the ITT sample size of 250. To preserve the overall type I error rate at the 1-sided significance level of 0.025, O'Brien-Fleming boundaries will be used. A detailed alpha spending scheme will be provided in the statistical analysis plan.

9.4.3.3. Supportive Secondary Analyses

Overall Survival in the ITT-Pembrolizumab population is defined according to the same criteria as OS in the ITT population. OS in the ITT-Pembrolizumab population will be compared between treatment arms using a stratified log-rank test, stratified by the randomization strata. The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. Overall survival curves, the median and survival rates at various time points with 95% CI, for each treatment arm will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

Progression-free survival per investigator assessment is defined according to the same criteria and will be analyzed using the same methodology as for BICR PFS.

Overall response rate (ORR) is defined as the number of patients who achieve a best overall response (BOR) of CR or PR divided by the total number of patients randomized to each treatment arm. Intracranial ORR is defined as the number of patients who achieve CR or PR of intracranial lesions divided by the total number of patients with baseline brain metastases and randomized to each treatment arm. The ORR and intracranial ORR, with 95% CI, will be summarized for each treatment arm. Best overall response is determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR.

Overall response rate and intracranial ORR will be compared between Arm A and Arm B using a Cochran-Mantel-Haenszel test stratified by the randomization strata. The ORR according to both BICR and investigator-assessed BOR will be evaluated per RECIST 1.1 criteria. Intracranial ORR will be assessed by BICR (no investigator assessment) per RECIST 1.1 and RANO-BM criteria.

Duration of response (DOR) is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or documented disease progression is observed, or the date of death from any cause in the absence of documented disease progression or recurrence. The DOR according to both BICR and investigator-assessed BOR will be evaluated per RECIST 1.1 criteria. Intracranial DOR will be assessed by BICR (no investigator assessment) per RECIST 1.1 and RANO-BM criteria.

Disease control rate (DCR) is defined as the number of patients who achieve a best overall response of CR, PR, or SD lasting 16 or more weeks divided by the total number of patients

randomized to each treatment arm. The DCR according to both BICR and investigator-assessed BOR will be evaluated.

Time to CNS progression is defined as the time from randomization to the occurrence of documented CNS progression by the BICR. Central nervous system progression is defined as progression due to newly developed intracranial lesions and/or progression of pre-existing intracranial lesions per RECIST 1.1. Non-CNS progression and death are completing events, because once a patient has systemic disease progression or death, no further scans are required per protocol. Time to CNS progression will be compared between Arm A and Arm B using a stratified log-rank test, computed on the basis of cause-specific hazard functions. The corresponding cause-specific HRs will be estimated using a stratified Cox regression model. Gray's test (Gray 1988; Fine and Gray 1999) to compare the risk of CNS progression between treatment arms will also be performed.

Progression-free survival 2 is defined as the time from randomization to disease progression on the next line of treatment or death from any cause in the absence of observed disease progression. If the patient is alive at the cutoff date for the analysis, and disease progression has not been observed, PFS2 data will be censored on the latest date of last progression-free assessment or start of the next line of treatment.

Time to deterioration in pulmonary symptoms assessed by NSCLC-SAQ will be described using the method of Kaplan-Meier and a comparative analyses between the 2 arms using a log-rank test. Further details will be provided in the SAP.

The error-controlled testing strategy of supportive secondary endpoints will be described in the SAP.

9.4.4. Safety Analyses

The safety population will consist of all randomized patients who receive at least 1 dose of any study drug(s). A baseline measurement and at least 1 laboratory or other safety-related measurement obtained after treatment of study drug may be required for inclusion in the analysis of a specific safety parameter. The safety analyses will be performed on the patients who receive at least 1 dose of any study drug in the ITT-pembrolizumab population and in the ITT population.

The IDMC will monitor the overall safety of the study. An early safety analysis will be performed after approximately 50 patients have been randomized and had the opportunity to be treated for 2 cycles. The IDMC will meet and review data approximately every 6 months thereafter. Detailed information on the role of the IDMC and frequency of meetings will be provided in the IDMC charter separate from this protocol.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

Selpercatinib plasma concentrations will be summarized by descriptive statistics. Additional analysis utilizing the population PK approach may also be conducted if deemed appropriate.

The relationship between selpercatinib plasma exposure and selected efficacy and safety outcomes may be explored.

9.4.6. Other Analyses

9.4.6.1. Patient-Reported Outcomes and Health Care Resource Utilization

For each instrument, percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments. Data will be separately summarized using descriptive statistics.

Further details will be provided in the SAP for each patient-reported outcome (PRO) instrument, respectively.

Frequency counts of hospitalizations, emergency room visits, G-CSF use, transfusions, and analgesic use will be reported descriptively for each treatment arm by cycle.

9.4.6.2. Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for OS, PFS, and ORR (with a nominal 95% CI) will be estimated and plotted within each category of the following subgroups (defined based on eCRF data):

- Age category (≤65 vs. >65 years)
- ECOG Performance Scale (0 to 1 vs. 2)
- Sex (female vs. male)
- Race (Asian vs. non-Asian)
- Geography (East Asia vs. non-East Asia)
- Smoking status (never vs. former/current smokers)
- Brain metastasis status at baseline (absence or unknown vs. presence)
- Disease stage (Stage IVA vs. Stage IVB)
- PD-L1 expression (TPS <1% vs. TPS ≥1% vs. unknown)
- Liver metastases (absence vs. presence)
- Tissue vs. blood *RET* fusion detection
- *KIF5B* vs. no-*KIF5B* fusion partner
- Investigator's choice of treatment with vs. without pembrolizumab

If a level of a factor includes fewer than 5% of the ITT population, analysis within that level will be omitted. Additional subgroup analyses may be performed as deemed appropriate.

9.4.6.3. Biomarker Analysis

Biomarker results will be summarized and may be analyzed for correlations with clinical outcomes.

9.4.6.4. Evaluation of *RET* Testing Results

The consistency between the *RET* results based on local laboratory tests and a single, central test will be evaluated to assess the performance of *RET* fusion testing at local laboratories.

9.4.6.5. PFS/ORR/DOR/DCR after Crossover

Progression-free survival after crossover in patients randomly assigned to Arm B who crossed over to selpercatinib is defined as the time from start of selpercatinib treatment until the occurrence of disease progression or death from any cause. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment. Overall response rate is defined as the number of patients who achieve a BOR of CR or PR with respect to the crossover baseline tumor assessment, divided by the total number of patients who assigned to Arm B and crossed over to selpercatinib. Duration of response is defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or documented disease progression is observed, or the date of death from any cause in the absence of documented disease progression or recurrence during crossover period. Disease control rate is defined as the number of patients who achieve a BOR of CR, PR, or SD lasting 16 or more weeks, divided by the total number of patients who assigned to Arm B and crossed over to selpercatinib. Further details will be provided in the SAP.

9.5. Interim Analyses

A single interim efficacy analysis for BICR PFS is planned at 67% information fraction (approximately 93 events) in the ITT-pembrolizumab population. The sequential monitoring approach of Lan and DeMets (1983) with the O'Brien-Fleming function will be used to control the type I error rate associated with the multiple looks. The event numbers, cumulative type I error rates, critical values and associated boundary crossing probabilities are provided in the table below. The HR and p-value boundaries are for reference only and they will be updated based on the actual number of events observed at the time of interim and final analysis. The interim boundary associated with the O'Brien-Fleming spending function was specifically chosen within the present context because it is generally considered conservative in terms of declaring early success at interim. This is desirable as there are substantial risk-benefit considerations beyond the primary endpoint. It is important to note that the interim HR boundary of 0.575 corresponds to a minimum of approximately 7 additional months of mPFS and a p-value < 0.006, indicating a stringent threshold for clinically/statistically significant PFS findings required to conclude success at interim analysis. With the O'Brien-Fleming function, there is an approximately 54% chance of the correct conclusion of early success under the alternative hazard ratio assumption of 0.563.

At the interim analysis, the other primary endpoint BICR PFS in the ITT population will only be tested if interim success is achieved in the ITT-pembrolizumab population. The observed number of events and corresponding boundary are to be updated at the time of analysis. Further details will be provided in the SAP.

Planned Analysis Stopping Rules

Analysis	Number of Events	Information Fraction	Cumulative Type I Error Probability	Critical HR Boundary	Critical p-Value Boundary	Boundary Crossing Probabilities	
						H_0: $HR = 1$	H_1: $HR = 0.563$
Interim	93	67%	0.006	0.575	0.006	0.006	0.540
Final	140	100%	0.025	0.700	0.023	0.019	0.351

Abbreviations: H0 = null hypothesis; H1 = alternative hypothesis; HR = hazard ratio.

The interim efficacy and overall safety of this study will be monitored by an IDMC. Efficacy will be evaluated based on prespecified stopping rules in the preplanned interim analyses. If the criterion for early efficacy is met at the time of an interim analysis, the IDMC may recommend stopping the study in accordance with the terms of the IDMC charter.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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) GCP Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for 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/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
    - Reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/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, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- 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 ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data . Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's 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 the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.
- The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.
- The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.4. Committee Structure

The primary endpoint, PFS, will be assessed by BICR. Blinded independent central review will consist of independent radiologists to perform response assessments and determination of disease progression per RECIST 1.1.

10.1.5. Dissemination of Clinical Study Data

Dissemination of study data will be performed according to all applicable Lilly and international policies.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

10.1.6. Data Quality Assurance

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

In addition, the sponsor or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, electronic Clinical Outcome Assessment (eCOA) data questionnaires and scales will be directly recorded by the patient, into an instrument (e.g., an electronic device). The eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

Data collected via the sponsor-provided data capture system will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and results will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

10.1.7. 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 in the 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.

10.1.8. Study and Site Closure

10.1.8.1. Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.8.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.9. Provisions for Changes in Study Conduct During Emergencies

There may be times due to exceptional circumstances where it may not be feasible for patients to come to investigator sites for study-required visits. To mitigate the risk of patients missing visits to allow patients to safely continue to receive care and maintain the data integrity of the study,

the following may be allowed on a case-by-case basis following approval from the sponsor and if permitted by local regulations:

- Remote/virtual visits and/or extended visit windows may be used. Medically qualified site personnel may collect study required information (e.g., AEs, concomitant medications, ECOG status, and study treatment compliance) via videoconference (preferred) or phone. Visit or cycle windows as defined in the schedule of activities may be extended to facilitate the ability to perform study-specific assessments at the site, which is preferred to remote/virtual visits. Every effort should be made to return to in-clinic visits as soon as reasonably possible and safe for the patient and investigator/site staff.
- Labs, ECGs and/or tumor imaging may be obtained at a local (nonstudy) site. Laboratory results (including reference ranges), ECGs and/or scans obtained at a local lab must be filed and reviewed by the study investigator or qualified designee in a timely manner.
- For patients that meet the protocol criteria to continue or restart dosing, local processes may be leveraged to deliver drug directly to patients. Note that the IV agents on Arm B must be administered at the clinic.
- A remote informed consent process may be implemented.

Site personnel are responsible for documenting in the source records all changes in study conduct, relevant communications (patient and sponsor), and dispensing/shipment records of IP and indicating the actions taken as a result of exceptional circumstances mitigation. If mitigations are approved by the sponsor, additional instructions on the process and documentation will be provided to the site. Additional mitigations may be approved by the sponsor and will be tracked as protocol deviations as required.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the indicated laboratory.
- Local laboratory results are required only in the event that the central laboratory results are not available in time for inclusion/exclusion determination, study intervention administration, and/or response evaluation. If a local sample is required or used for treatment decisions (e.g., delay the start of a cycle), it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, this should be reported into the CRF as an AE. If there is an abnormal laboratory value or abnormal value for any other diagnostic or screening test (e.g., blood pressure increased, neutrophils decreased, etc.) and it is known to be related to a diagnosis (e.g., hypertension, neutropenia, etc.) this should be reported into the CRF as an AE. Do not enter the test abnormality, enter the disease diagnosis or categorical term.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations, and clinically significant findings should be reported in the CRF as an AE.

Enrollment and treatment decisions may be based upon local laboratory results. Discrepancies between local and central laboratory results will not be considered a protocol deviation.

Clinical Laboratory Tests	
Hematology[a] **–** Local laboratory	
Leukocytes (WBC)	Basophils
Neutrophils	Erythrocytes (RBC)
Lymphocytes	Hemoglobin (HGB)
Monocytes	Hematocrit (HCT)
Eosinophils	Platelets (PLT)
Coagulation[a] **–** Local laboratory	
PT/INR	PTT/aPTT
Clinical chemistry[b,c] – Central laboratory	
Serum concentrations of:	
Alanine aminotransferase (ALT)	Chloride
Albumin	Creatinine
Alkaline phosphatase	Glucose (random)
Aspartate aminotransferase (AST)	Magnesium
Bilirubin, direct	Potassium
Bilirubin, total	Protein
Blood urea nitrogen (BUN) or blood urea	Sodium
Calcium	
Hepatic monitoring – Central laboratory[b]	
Alanine aminotransferase (ALT)	Bilirubin, direct
Aspartate aminotransferase (AST)	Bilirubin, total
Alkaline phosphatase	
Urinalysis[a] – Local laboratory	
Blood	Protein
Glucose	Specific gravity
Ketones	Urine leukocyte esterase[d]
pH	
Pregnancy Test[e] **–** Local laboratory	
Urine pregnancy test	Serum pregnancy test
Thyroid panel[b] - Central laboratory	
Triiodothyronine (T3)	Thyroid-stimulating hormone (TSH)
Thyroxine (T4)	

Abbreviations: aPTT = activated partial thromboplastin time; CRF = case report form; PT/INR = prothrombin time/international normalized ratio; PTT = partial thromboplastin time; RBC= red blood cell; WBC = white blood cell.

[a] Local or investigator-designated laboratory.

[b] Treatment and enrollment decisions may be based on local laboratory results. Investigators may use central laboratory results to guide treatment and enrollment decisions if local laboratories are not available. Local laboratory results are not required to be recorded on a CRF if a sample is sent to the central laboratory at the same time.

Note: Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and reported on the CRF, unless the CRF specifically provides an entry field for bands.

[c] Central laboratory may be used for Lilly investigational analysis.

[d] Urine microscopy may be used in the place of the urine leukocyte esterase assessment to test for the presence of WBCs.

[e] For female patients of childbearing potential.

10.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
   - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] that Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Vasectomized partner • *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] that Are User Dependent

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  ○ oral
  ○ intravaginal
  ○ transdermal
  ○ injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  ○ oral
  ○ injectable

• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

Collection of Pregnancy Information

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive selpercatinib.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed up to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.2. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with the Lilly CRP/CRS, or his/her designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Antinuclear Antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth Muscle Antibody (or Anti-actin Antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability, this may include HBV/HCV DNA or RNA.

10.5. Appendix 5: Restricted and Prohibited Concomitant Medication

The following table(s) describes the drug class and associated medications that will be prohibited, restricted, or be used with caution during the study treatment period. Patients who, in the assessment by the investigator, require the use of any of the prohibited treatments for clinical management should be removed from the study. In general, all strong and moderate CYP3A4 inhibitors, strong and moderate inducers of CYP3A4, sensitive CYP2C8 substrates, and proton pump inhibitors (PPI's) are to be used with caution during the study treatment period. Agents known to cause QTc prolongation are prohibited during the study treatment period. Please see Section 6.5 for additional information.

This is not an all-inclusive list.

Note: Nonsystemic (e.g., topical creams, eye drops, mouthwashes, etc.) applications of the following are permissible.

Inhibitors of CYP3A4	
Strong Inhibitors[a]	**Moderate Inhibitors[b]**
boceprevir	amprenavir
clarithromycin	atazanavir
conivaptan	ciprofloxacin
grapefruit juice[c]	darunavir
indinavir	diltiazem
itraconazole	erythromycin
ketoconazole	fluconazole
lopinavir	fosamprenavir
mibefradil	imatinib
nefazodone	verapamil
nelfinavir	
posaconazole	
ritonavir	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

Abbreviations: AUC = area under the concentration versus time curve; CYP3A4 = cytochrome P450 3A4.

[a] Increases the AUC of sensitive index substrates of a given metabolic pathway by ≥5-fold.

[b] Increases the AUC of sensitive index substrates of a given metabolic pathway by 2- to 5-fold.

[c] When excessive amounts are consumed.

Inducers of CYP3A4	
Strong Inducers[a]	**Moderate Inducers**[b]
Avasimibe	bosentan
carbamazepine	efavirenz
Enzalutamide	etravirine
Phenytoin	modafinil
Rifampin	nafcillin
St John's wort	

Abbreviations: AUC = area under the concentration versus time curve; CYP3A4 = cytochrome P450 3A4.

[a] Decreases the AUC of the sensitive index substrates of a given metabolic pathway by ≥80%.

[b] Decreases the AUC of the sensitive index substrates of a given metabolic pathway by 50% to 80%.

Sensitive CYP2C8 substrates
Repaglinide
Dasabuvir
Selexipag

Abbreviation: CYP2C8 = Cytochrome P4502C8.

Examples of PPIs	
omeprazole	pantoprazole
esomeprazole	rabeprazole
lansoprazole	dexlansoprazole

Abbreviation: PPI = proton pump inhibitor.

Examples of H2 blocking agents	
famotidine	cimetidine
ranitidine	nizatidine

Note: The above lists are not exhaustive.

See also:
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.

Examples of Agents Known to Cause QTc Prolongation	
Amiodarone	ibogaine
Anagrelide	ibutilide
Azithromycin	levofloxacin
Chloroquine	levomepromazine (methotrimeprazine)
Chlorpromazine	levosulpiride
Cilostazol	methadone
Ciprofloxacin	moxifloxacin
Citalopram	ondansetron
Clarithromycin	papaverine HCl (intracoronary)
Cocaine	pentamidine
Disopyramide	pimozide
Dofetilide	procainamide
domperidone	propofol
Donepezil	quinidine
Dronedarone	roxithromycin
Droperidol	sevoflurane
Erythromycin	sotalol
Escitalopram	sulpiride
Flecainide	sultopride
Fluconazole	terlipressin
halofantrine	terodiline
Haloperidol	thioridazine
hydroquinidine, dihydroquinidine	

Note: The above list is not exhaustive.

10.6. Appendix 6: Country-Specific Requirements

Discontinuation of Inadvertently Enrolled Patients in the United Kingdom and Germany

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow up should be performed as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

Time Period and Frequency for Collecting SAE information for Patients in Germany

All SAEs, regardless of causality, should be reported for the entire duration of the clinical trial. Since survival is a secondary endpoint and patients are followed after discontinuation of study treatment, SAEs should be reported until patient death.

Hepatitis B, Hepatitis C and HIV testing for Patients in Germany:

If the HIV, Hepatitis B, or Hepatitis C status is not known, suitable testing should be carried prior to the initiation of therapy to determine if exclusion criteria 16 or 17 are met.

10.7. Appendix 7: Creatinine Clearance Formula

Note: This formula has to be used for calculating CrCl from local laboratory results only.

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}) \times 0.85 \text{ (if female), or } \times 1.0 \text{ (if male)}}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^{a}) \times (\text{wt}) \times 0.85 \text{ (if female), or } \times 1.0 \text{ (if male)}}{0.81 \times \text{serum creatinine (μmol/L)}}$$

[a] Age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product
BICR	blinded independent central review
BID	twice a day
BOR	best overall response
BSA	body surface area
BUN	blood urea nitrogen,
CAP	College of American Pathologists
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.

Term	Definition
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	clinical research scientist
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria in Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EORTC	European Organisation for Research and Treatment of Cancer Quality of Life questionnaire
EORTC IL19	European Organisation for Research and Treatment of Cancer item library 19

Term	Definition
EQ-5D-5L	EuroQol Five Dimension Five Level
ERB	ethical review board
ESMO	European Society for Medical Oncology
FACT-GP5	Functional Assessment of Cancer Therapy-Side Effects
FNA	fine needle aspiration
FSH	follicle-stimulating hormone
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GDPR	EU General Data Protection Regulation
GFR	glomerular filtration rate
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IMP	investigational medicinal product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

Term	Definition
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune Response Evaluation Criteria in Solid Tumors
ISO/IEC	International Organization for Standardization/Independent Ethics Committee
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
LFT	Liver function test
LNRH	Luteinizing hormone-releasing hormone
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MKI	multikinase inhibitor
mPFS	median progression-free survival
MRI	magnetic resonance imaging

Term	Definition
MTC	medullary thyroid cancer
NGS	next generation sequencing
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein 1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PPI	Proton pump inhibitor
PR	partial response
PRO	patient-reported outcomes
QD	once daily
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAQ	Symptom Assessment Questionnaire
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

Term	Definition
SoA	schedule of activities
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious, and as having a reasonable possibility of a causal relationship with the study intervention.
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TKI	tyrosine kinase inhibitor
TPS	tumor proportion score
UK	United Kingdom
ULN	upper limit of normal
WOCBP	woman of childbearing potential

10.9. Appendix 9: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment (d)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment incorporates changes to include additional endpoints to further characterize the intracranial activity of selpercatinib compared to the control arm. In addition, this amendment includes changes made to correct and clarify information for sites. This amendment also corrects typographical errors and inconsistencies that were noted in Study JZJC amendment (c).

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated newly added endpoints to match the updated endpoints in Section 3	To align with Section 3
1.2 Schema and throughout	Changed coprimary to primary or deleted coprimary	To align with intent of original protocol; only one of the endpoints needs to be positive, not both
1.3 Schedule of Activities Prescreening	Added information about the possibility of using a fresh biopsy to determine eligibility to the schedule of activities	Clarification
1.3 Schedule of Activities Main and crossover	Deleted the requirement for ECG to be obtained after Cycle 6	To align with IB
1.3 Schedule of Activities Main and crossover	Added Karnofsky performance status	To enable intracranial assessment by RANO-BM
1.3 Schedule of Activities Main and crossover	Intracranial evaluation with CT or MRI is required for all patients	To align with newly added endpoints
1.3 Schedule of Activities	Note regarding blood sample for pharmacokinetics was corrected	Correction to align with schedule
1.3 Schedule of Activities Main	Information regarding archived tumor tissue or fresh biopsy was moved to the screening visit	To clarify that a biopsy may be obtained during screening to determine eligibility
3 Objectives and Endpoints	Included additional endpoints	In order to evaluate the potential protective effect of selpercatinib to prevent or delay brain

Section # and Name	Description of Change	Brief Rationale
		metastases To describe efficacy after crossover with additional endpoints
4.1 Overall Design And 9.4.3.1. Primary Analysis	Added language to indicate the study will be considered positive if a statistically significant improvement in PFS by BICR in the ITT-pembrolizumab population is observed	Clarification
5.2 Exclusion criteria (criterion 25) And 6.5.1 Prohibited Concomitant Therapy	Added "The use of topical, ophthalmic, inhaled, and intranasal corticosteroids is permitted."	Clarification
6.5.1 Prohibited Concomitant Therapy	Added statement that changes in steroid use/doses should be recorded in eCRF	To facilitate assessment of RANO-BM
8.1.1 Imaging	Added recommendation to confirm presence of malignant cells before determining progressive disease on imaging alone	For consistency with the IB
8.1.2 BICR assessment	Added RANO-BM assessment	For the evaluation of CNS related endpoints
9.4.3.3 Supportive Secondary Analyses	Added information about how the newly added endpoints would be analyzed	To align with new endpoints
9.4.6.2 Subgroup Analyses	Added refinements to subgroup analyses	Remove the subgroups that are not feasible based on current data collection
9.4.6.5 PFS/ORR/DOR/DCR after Crossover	Added definition for newly added endpoints	To align with new endpoints

Amendment (c)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Overall Rationale for the Amendment:

This amendment corrects typographical errors and inconsistencies that were noted in JZJC amendment (b).

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated rationale regarding immunotherapy	Updated text to be consistent with

Section # and Name	Description of Change	Brief Rationale
		Section 4.2
1.3 SOA	Adjusted timing and description of PRO	Correction and clarifications
1.2 Schema and 4.1 Overall Design	Corrected language regarding percentage of patients with intent to not receive pembrolizumab	Typographical error
4.1 Overall Design	Modified language of testing strategy for coprimary and secondary endpoints	Clarification
1.1 Synopsis and 3 Objectives and Endpoints	Clarified endpoints and description of PRO objectives and updated secondary endpoints in Objectives/Endpoints Table	Clarification
8.3 AE and SAE	Removed conflicting language	Clarification
8.9.1. Patient Reported Outcomes and Health Care Resource Utilization	Updated health-related quality of life assessments	Clarification
9.2 Sample Size Determination	Clarified language regarding percentage of patients with intent to not receive pembrolizumab	Clarification
9.4.3.2 Key Secondary Analyses and 9.4.3.3 Supportive Secondary Analyses	Clarified OS testing strategy; Added targeted number of deaths for final OS analyses	Clarification
9.4.3.3 Supportive Secondary Analyses	Added language of analyzing methodology for PFS by investigator. Added OS definition in the ITT pembro population and moved disease control definition after duration of response	Clarification
9.4.6.1. Patient Reported Outcomes and Health Care Resource Utilization	Moved Kaplan-Meier method assessment to section 9.4.3.3.	Clarification
9.4.6.4. Evaluation of RET-Testing Results	Modified language of RET-testing evaluation	Clarification
9.4.6.5. PFS after Crossover	Added this section for consistency with Section 3, where PFS after crossover is one of the exploratory endpoints	Clarification
9.5 Interim Analysis	Added how to update the boundaries at analysis	Clarification
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore not detailed

Amendment (b)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Overall Rationale for the Amendment:

This amendment incorporates changes requested by regulatory agencies. In addition, this amendment includes changes made to correct and clarify information for sites.

Section # and Name	Description of Change	Brief Rationale
Section 1.1. Synopsis (Objectives and Endpoints)	Updated primary objective; updated secondary objectives and end points	To meet country-specific regulatory and payer expectations
Section 1.1. Synopsis (Overall Design)	Added a sentence related to randomization ratio	Minimize patients treated on control arm (based on regulatory agency feedback and LIBRETTO-001 data)
Section 1.1. Synopsis (Overall Design)	Changed primary endpoint	Clarification
Section 1.1. Synopsis (Number of Participants)	Updated number of participants	Minimize patients treated on control arm (based on regulatory agency feedback and LIBRETTO-001 data)
Section 1.2. Schema	Updated sample size, randomization, and primary objective; modified footnote a and added footnote c	Based on regulatory agency feedback and payer expectations
Section 1.3. Schedule of Activities	Added test results language to instructions for prescreening ICF	To clarify that *RET* is not the only result that will be provided
Section 1.3. Schedule of Activities	Updated archived tumor or fresh biopsy and optional postprogression tumor biopsy collection instructions	Clarification
Section 1.3. Schedule of Activities	Duration of ECG monitoring update	For consistency with updated IB
Section 1.3. Schedule of Activities	Clarified hepatic safety monitoring also includes direct bilirubin	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Updated sample collection timelines for PK instructions	To provide more flexibility based on feasibility feedback from sites
Section 1.3. Schedule of Activities	Duration of ECG monitoring update in crossover SOA	For consistency with updated IB
Section 1.3. Schedule of Activities	Updated timing of radiologic imaging and measurement of palpable or visible lesion instructions in crossover SoA	To match the expectations in main protocol
Section 1.3. Schedule of Activities	Clarified instructional guidance for intracranial evaluation with CT or MRI in crossover SoA	Clarification
Section 1.3. Schedule of Activities	Updated sample collection timelines for PK instructions in crossover SoA	To provide more flexibility based on feasibility feedback from sites
Section 1.3. Schedule of Activities	Correction of time point and clarified hepatic safety monitoring also includes direct bilirubin in crossover SoA	Clarification
Section 1.3. Schedule of Activities	Corrected the instructional guidance for EQ-5D-5L in crossover SoA	Correction
Section 1.3. Schedule of Activities	Added note related to usage of crossover baseline/screening assessments	Clarification
Section 1.3 Schedule of Activities	Modified language around scan submissions	Clarification
Section 1.3 Schedule of Activities	Added premedication procedure to screening period	Clarification
Section 1.3 Schedule of Activities	Updated table notes for baseline/screening assessments during on-study treatment period	Clarification
Section 3. Objectives and Endpoints	Updated primary objective; updated secondary objective and end points; added tertiary/exploratory objective	To meet country-specific regulatory and payer

Section # and Name	Description of Change	Brief Rationale
	and end point related to PK	expectations
Section 4.1. Overall Design	Updated sample size, stratification factor related to platinum therapy, randomization, primary endpoint, and number of patients that will be assigned to treatment without pembrolizumab	To meet country-specific regulatory and payer expectations and based on additional LIBRETTO-001 data
Section 4.2. Scientific Rationale for Study Design	Modified pembrolizumab language	Updated based on recent publications and data
Section 5.1. Inclusion Criteria	Clarified language for histological diagnosis in Inclusion Criterion 1	Clarification
Section 5.1. Inclusion Criteria	Removed tissue sample requirements in Inclusion Criterion 2	Based on a change in regulatory agency requirements
Section 5.1. Inclusion Criteria	Specified timeline for organ function lab values in Inclusion Criterion 6	Clarification
Section 5.1. Inclusion Criteria	Modified language on male contraception in Inclusion Criterion 8	Based on regulatory agency feedback
Section 5.1. Inclusion Criteria	Removed legally authorized representative from informed consent requirements	Clarification
Section 5.2. Exclusion Criteria	Modified pleural effusion language in Exclusion Criterion 15	Clarification
Section 5.2. Exclusion Criteria	Updated Hepatitis B and C status in Exclusion Criterion 17	Based on investigator feedback and newly published guidance
Section 5.2. Exclusion Criteria	Added in situ cancers as exceptions to Exclusion Criterion 20	Clarification
Section 5.2. Exclusion Criteria	Updated prior therapy criteria in Exclusion Criterion 21	Based on investigator feedback
Section 5.2. Exclusion	Exclusion Criteria 23 and 24	New data indicated these

Section # and Name	Description of Change	Brief Rationale
Criteria	removed due to change in study design	exclusions were not required
Section 5.2. Exclusion Criteria	Clarified steroid treatment definition in Exclusion Criterion 25	Clarification
Section 5.2. Exclusion Criteria	Clarified prior treatment	Clarification
Section 6.1.1 Selection and Timing of Doses	Added pre- or postmedication guidance	Clarification
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	Clarified stratification factor related to investigator's choice of treatment	Clarification
Section 6.5.1. Prohibited Concomitant Therapy	Updated steroid treatment language and removed CYP3A4 inhibitors as prohibited concomitant use	New data resulted in updated guidance
Section 6.5.1. Prohibited Concomitant Therapy	Updated steroid treatment exclusions	Clarification
Section 6.5.1.1. Concomitant Therapy Considerations for Arm A	Modified language regarding concomitant therapy with PPIs and CYP3A inhibitors	New data resulted in updated guidance
Section 6.5.1.1. Concomitant Therapy Considerations for Arm A	Deleted language on discontinuation of CYP3A4 inducer prior to study administration	New data resulted in updated guidance
Section 6.5.2. Palliative Medicine and Supportive Care for Arms A and Arm B	Removed sentence related to needing sponsor approval for physiologic dose of corticosteroid usage and updated study drug half-lives before and after RT or surgery	Sponsor approval is not needed and clarification
Section 6.5.2. Palliative Medicine and Supportive Care for Arm A and Arm B	Added guidance for patients with hepatitis B or C	Based on investigator feedback and newly published guidance

Section # and Name	Description of Change	Brief Rationale
Section 6.6. Dose Modification Guidelines for Arm a and Arm B	Added dose reduction and re-escalation instructions and updated Dose reduction for study interventions table	Clarification
Section 6.6. Dose Modification Guidelines for Arm a and Arm B	Updated Dose reduction for study interventions table and updated footnote for Dose Level 3 discontinuation	Clarification
Section 6.6.1. Dose Modifications and Toxicity Management Guidelines for Arm A	Removed recommended lab testing for selpercatinib drug hypersensitivity; updated dose modifications for selpercatinib liver function test abnormalities; updated dose modifications for thrombocytopenia; updated dose modifications for hypertension; amended dose modification guidelines for patients on Arm A	For consistency with updated IB
Section 8.1.1. Imaging	Clarified scan interval schedule	Clarification
Section 8.2.1. Electrocardiograms	Clarified QTcF values that require action	Clarification
Section 8.5. Pharmacokinetics	Updated sample collection time point	Clarification and consistency with SoA.
Section 8.8.1. Samples for Retrospective Evaluation of RET Status	Modified sample language and removed required slides to determine *RET* status; added language around results of testing	Based on a change in regulatory agency requirements
Section 8.8.2. Biomarkers	Added language related to whole blood collection	Clarification
Section 8.9.1. Patient-reported Outcomes and Health Care Resource Utilization	Modified language around completing questionnaires	Clarification
Section 9.1. Statistical Hypotheses	Updated primary hypothesis	To meet country-specific regulatory and payer

Section # and Name	Description of Change	Brief Rationale
		expectations
Section 9.2. Sample Size Determination	Updated language around sample size, randomization and cap on investigator's choice of chemotherapy and coprimary endpoints	Minimize patients treated on control arm (based on regulatory agency feedback and LIBRETTO-001 data)
Section 9.3. Populations for Analyses	Updated description of the ITT-pembrolizumab population	Clarification
9.4.3. Efficacy Analyses	Revised efficacy analyses population	Clarification
Section 9.4.3.1. Primary Analysis	Amended details related to the primary analysis	To meet country-specific regulatory and payer expectations
Section 9.4.3.2. Secondary Analysis	Amended details related to numerous secondary analyses	To meet country-specific regulatory and payer expectations
Section 9.4.4. Safety Analyses	Clarified population to perform safety analyses on	Clarification
Section 9.5 Interim Analyses	Added a single interim efficacy analysis and provided details for this analysis; removed previously described interim analyses	To meet country-specific regulatory and payer expectations
Section 10.2. Appendix 2: Clinical Laboratory Tests	Updated required sample instructions for treatment decisions and local lab results recording	
Section 10.5. Appendix 5: Restricted and Prohibited Concomitant Medication	Added guidance related to CYP usage	For consistency with updated IB
Section 10.5. Appendix 5: Restricted and Prohibited Concomitant Medication	Modified list of moderate CYP3A4 inhibitors	Correction
Section 10.5. Appendix	Removed guidance related to	For consistency with updated

Section # and Name	Description of Change	Brief Rationale
5: Restricted and Prohibited Concomitant Medication	timeframe of PPI usage	IB
Section 10.6. Appendix 6: Country-Specific Requirements	Added guidance related to SAE collection for German patients	To meet country-specific regulatory requirements
Section 10.6. Appendix 6: Country-Specific Requirements	Added guidance related to Hepatitis and HIV testing for German patients	To meet country-specific regulatory requirements
Throughout the protocol	Changed the name of LOXO-292 to selpercatinib	Regulatory approval of drug name
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore not detailed

Amendment (a)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Overall Rationale for the Amendment:

This amendment incorporates changes requested by regulatory agencies. In addition, this amendment includes changes made to correct and clarify information for sites.

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	Added requirement for adequate tissue for central confirmation and removed FISH as a possible testing method; added inclusion criteria related to breast-feeding	Based on regulatory agency feedback
3. Objectives	Added secondary objective to assess/evaluate performance of *RET* local laboratory tests compared to a single, central test	Based on regulatory agency feedback
9.4.6.4. Evaluation of *RET*	Added subsection regarding evaluation of RET testing	Based on regulatory agency

Section # and Name	Description of Change	Brief Rationale
Testing Results	results	feedback
8.8. Biomarkers	Updated samples required for eligibility section regarding mandatory tissue requirements for central *RET* fusion confirmation	Based on regulatory agency feedback
2.3. Benefit Risk Assessment	Added additional information and context to risk benefit assessment	Based on regulatory agency feedback
5.1. Inclusion Criteria	Modified Contraception section to indicate participants must use a highly effective method of contraception and align with pemetrexed label language; modified Informed Consent section regarding language on participant's ability to understand implications of participation in a trial	Based on regulatory agency feedback
5.2. Exclusion Criteria	Modified Medical Condition section. Clarified HIV and Hepatitis B exclusion criteria	Based on regulatory agency feedback
6.5. Concomitant Therapy	Modified language on vaccine administration	Based on regulatory agency feedback
6.6. Dose Modification for Arm A and Arm B	Modified recommended assessments following a hypersensitivity reaction	Based on regulatory agency feedback
1.3. Schedule of Activities	Added test range for pregnancy tests during study treatment	Based on regulatory agency feedback
5.1. Inclusion Criteria	Added clarification that all *RET* testing is required to be authorized by an appropriate accreditation body	Based on regulatory agency feedback

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Updated ECG instructions and added timepoints for Arm A and Arm B; added sponsor approval language for scan submission; updated archived tissue instructions, updated pharmacokinetics sample instructions; updated collection of cfDNA	Clarification
4.1. Overall Design	Clarified brain metastases assessment stratification language	Clarification
5.2. Exclusion Criteria	Clarified timing of prior neoadjuvant/adjuvant therapy	Clarification
10.5. Appendix	Added list of H2 blocking agents	Clarification
Throughout the protocol	Updated drug name to selpercatinib	Clarification
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore not detailed

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Approval	PPD Medical Director 14-Aug-2023 13:57:54 GMT+0000

Approval	PPD Statistician 15-Aug-2023 14:37:41 GMT+0000

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