Official Title: A Phase III, Randomized, Open-Label Study of Pralsetinib Versus Standard of Care for First-Line Treatment of RET Fusion-Positive, Metastatic Non-Small Cell Lung Cancer

NCT Number: NCT04222972

Document Date: Protocol Amendment Version 6: 23-Oct-2024

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL STUDY OF PRALSETINIB VERSUS STANDARD OF CARE FOR FIRST-LINE TREATMENT OF RET FUSION–POSITIVE, METASTATIC NON–SMALL CELL LUNG CANCER**
PROTOCOL NUMBER:	BO42864
STUDY NAME	AcceleRET-Lung
VERSION NUMBER:	6
TEST PRODUCT:	Pralsetinib (RO7499790)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIERS:	IND Number: 143094 EudraCT Number: 2019-002463-10 EU CT Number: 2023-505035-12-00 NCT Number: NCT04222972
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd. Grenzacherstrasse 124 4058 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country and/or Region-Specific Protocols		
Version	**Date Final**	**Country and/or Region**	**Version**	**Date Final**
6	See electronic date stamp on the final page of this document.	—	—	—
5	3 April 2024	—	—	—
4	28 April 2022	—	—	—
3	29 January 2021	Ireland	3	27 July 2021
2	10 October 2019	Ireland	2	15 December 2020
1	27 August 2019	—	—	—

PROTOCOL AMENDMENT, VERSION 6:
RATIONALE

A review of fatal events in Study BO42864 for pralsetinib versus platinum-based standard of care identified an imbalance in fatal adverse events, in particular infectious fatal adverse events. Following this review, severe infections, including opportunistic infections, are now an identified risk with pralsetinib.

Protocol BO42864 has been amended to reflect changes in recommendations on monitoring participants for infection, pralsetinib dose interruption, reduction or permanent discontinuation, depending on severity of the adverse event. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- Text has been updated to include review findings of infectious fatal adverse events and management guidelines for pralsetinib (Sections A5-1.1.1 [Table A5-1] and A5-1.1.2 [Table A5-3]).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL STUDY OF PRALSETINIB VERSUS STANDARD OF CARE FOR FIRST-LINE TREATMENT OF RET FUSION-POSITIVE, METASTATIC NON-SMALL CELL LUNG CANCER**
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STUDY NAME:	AcceleRET-Lung
VERSION NUMBER:	6
TEST COMPOUND:	Pralsetinib (RO7499790)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, OPEN-LABEL, STUDY OF PRALSETINIB VERSUS STANDARD OF CARE FOR FIRST-LINE TREATMENT OF RET FUSION–POSITIVE, METASTATIC NON–SMALL CELL LUNG CANCER**
REGULATORY AGENCY IDENTIFIERS:	IND Number: 143094 EudaCT Number: 2019-002463-10 EU CT Number: 2023-505035-12-00 NCT Number: NCT04222972

STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of pralsetinib compared with standard-of-care (SOC) for the first-line treatment of patients with rearranged during transfection (RET) fusion–positive, metastatic non–small cell lung cancer (NSCLC). SOC treatment will be investigator's choice of SOC platinum-containing anticancer treatment regimens, as measured primarily by progression-free survival (PFS), for patients with RET fusion–positive metastatic NSCLC who have not previously received treatment with a multikinase inhibitor for metastatic disease.

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoint
• To assess whether pralsetinib improves PFS compared with investigator's choice of SOC platinum-containing anticancer treatment regimens for participants with RET fusion-positive metastatic NSCLC	• PFS, defined as the time from randomization date to the first documented PD, as assessed by investigator according to RECIST v1.1 or death due to any cause, whichever occurs first
Key Secondary Objectives	**Key Corresponding Endpoints**
• To evaluate the efficacy of pralsetinib compared with investigator's choice of SOC platinum-containing anticancer treatment regimens	• ORR, defined as the proportion of participants with a CR or a PR on two consecutive occasions $\geq$4 weeks apart, as assessed by investigator according to RECIST v1.1
• To evaluate OS	• OS, defined as the time from randomization date to death due to any cause
Additional Secondary Objectives	**Additional Corresponding Endpoints**
• To evaluate the safety and tolerability of pralsetinib compared with investigator's choice of SOC platinum-containing anticancer treatment regimens	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 • Change from baseline ECOG Performance Status • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results

• To compare additional measures of anticancer activity	• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as assessed by investigator according to RECIST v1.1 • CBR, defined as the proportion of participants who experience a best response of SD with a minimum duration of 6 months, a CR, or a PR, as assessed by investigator according to RECIST v1.1 • DCR, defined as the proportion of participants who experience a best response of CR, or PR, or SD, as assessed by investigator according to RECIST v1.1

CBR = clinical benefit rate; CR = complete response; CTCAE v5.0 = Common Terminology Criteria for Adverse Events, Version 5.0; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival;; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RET = rearranged during transfection (oncogene); SD = stable disease; SOC = standard of care.

OVERALL DESIGN AND STUDY POPULATION

The Sponsor has decided to prematurely terminate the study due to Blueprint Medicines' decision to discontinue global marketing and development of pralsetinib in all territories (excluding US and Greater China). The investigators were informed of premature study termination on 23 January 2024 by a study memo communicating this decision.

This is a Phase III, randomized, open-label, two-arm, international study designed to evaluate the efficacy and safety of pralsetinib compared with platinum chemotherapy-based regimen chosen by the investigator from a list of SOC platinum-containing anticancer treatment regimens.

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

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Active comparator	**Population Diagnosis or Condition:**	Locally advanced unresectable or metastatic NSCLC with documented RET fusion
Interventional Model:	Parallel	**Population Age:**	≥ 18 years
Test Product:	Pralsetinib (RO7499790)	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	• Carboplatin/cisplatin and pemetrexed; • Pembrolizumab, carboplatin/cisplatin, and pemetrexed; • Carboplatin/cisplatin and gemcitabine; or • Pembrolizumab, carboplatin, and paclitaxel or nab-paclitaxel	**Study Treatment Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 226

STUDY TREATMENT

Pralsetinib

Participants randomized to pralsetinib (Arm A) or participants originally randomized to Arm B who cross over will receive 400 mg pralsetinib by mouth once a day. Dosing will be continuous, with no inter-cycle rest periods. The dose of pralsetinib can be reduced up to three times for management of drug-related toxicities.

Standard of Care

Participants randomized to the chemotherapy arm (Arm B) will receive one of six SOC platinum-containing anticancer treatment regimens at the study center as chosen by the treating investigator on the basis of NSCLC histology.

- For participants with NSCLC of non-squamous histology:
  - Carboplatin in combination with pemetrexed (with vitamin supplementation): Participants should receive pemetrexed 500mg/m^2 followed by carboplatin to target area under the concentration–time curve (AUC) of 5 mg • min/mL both on Day 1 every 3 weeks (Q3W) for 4 or 6 cycles with an option to continue maintenance pemetrexed 500 mg/m^2 Q3W until progression or up to a maximum of 2 years.
  - Cisplatin in combination with pemetrexed (with vitamin supplementation): Participants should receive pemetrexed 500 mg/m2 followed by cisplatin 75 mg/m2 both on Day 1 Q3W for 4 or 6 cycles with an option to continue maintenance pemetrexed 500 mg/m^2 Q3W until progression or for up to a maximum of 2 years.
  - Pembrolizumab in combination with carboplatin and pemetrexed (with vitamin supplementation): Participants should receive pembrolizumab 200 mg together with pemetrexed 500 mg/m^2 (with vitamin supplementation) and carboplatin AUC of 5 mg/mL/min all on Day 1 Q3W for four to six cycles followed by pembrolizumab 200 mg together with pemetrexed 500 mg/m^2 Q3W until progression or for up to a maximum of 2 years.

  - Pembrolizumab in combination with cisplatin and pemetrexed (with vitamin supplementation): Participants should receive pembrolizumab 200 mg together with pemetrexed 500 mg/m^2 (with vitamin supplementation) and cisplatin 75 mg/m^2 all on Day 1 Q3W for 4 or 6 cycles followed by pembrolizumab 200 mg together with pemetrexed 500 mg/m2 Q3W until progression or for up to a maximum of 2 years.
- For participants with NSCLC of squamous histology, participants will receive one of following three SOC platinum-containing anticancer treatment regimens at the study center as chosen by the treating investigator:
  - Carboplatin in combination with gemcitabine: Participants should receive carboplatin to target AUC of 5 mg • min/mL on Day 1 of each 3-week cycle and gemcitabine 1250 mg/m^2 on Days 1 and 8 of each 3-week cycle for 4 or 6 cycles.
  - Cisplatin in combination with gemcitabine: Participants should receive cisplatin 75 mg/m^2 on Day 1 of every 3-week cycle and gemcitabine 1250 mg/m^2 on Days 1 and 8 of each 3-week cycle for 4 or 6 cycles.
  - Carboplatin in combination with paclitaxel/nab-paclitaxel and pembrolizumab: Participants should receive pembrolizumab 200 mg together with carboplatin to target AUC of 6 mg • min/mL and paclitaxel 200 mg/m^2 on Day 1, or nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 of each 3-week cycle for 4 or 6 cycles, followed by pembrolizumab 200 mg Q3W until progression or for up to a maximum of 2 years.

Each study site will administer chemotherapy for 4 or 6 cycles based on local guidelines.

Doses of investigator's choice of SOC platinum-containing anticancer therapy regimens may be modified or discontinued due to toxicity as described in the product labels and on institutional standards.

DURATION OF PARTICIPATION

The Sponsor has decided to prematurely terminate Study BO42864. The duration of participation for each participant will depend on the treatment received:

- Participants receiving pralsetinib can remain on the study until disease progression as assessed by the investigator, until continued access solutions for pralsetinib are available, pralsetinib is no longer available, or precluded by toxicity, non-compliance, withdrawal of consent, death, or closure of the study by the Sponsor, whichever comes first.
- Participants receiving SOC platinum-containing anticancer treatment should be withdrawn from the study promptly. In the event that the SOC treatment regimen used within the study is not available to the participant after withdrawal, the participant may remain in the study and continue to receive the SOC treatment but must discontinue, at the latest, by the time the last patient receiving pralsetinib has discontinued from the study. Investigators will be given advanced notice of this timepoint. Additional reasons for study discontinuation for participants that are eligible to remain in the study are toxicity, non-compliance, withdrawal of consent, death, or closure of the study by the Sponsor.

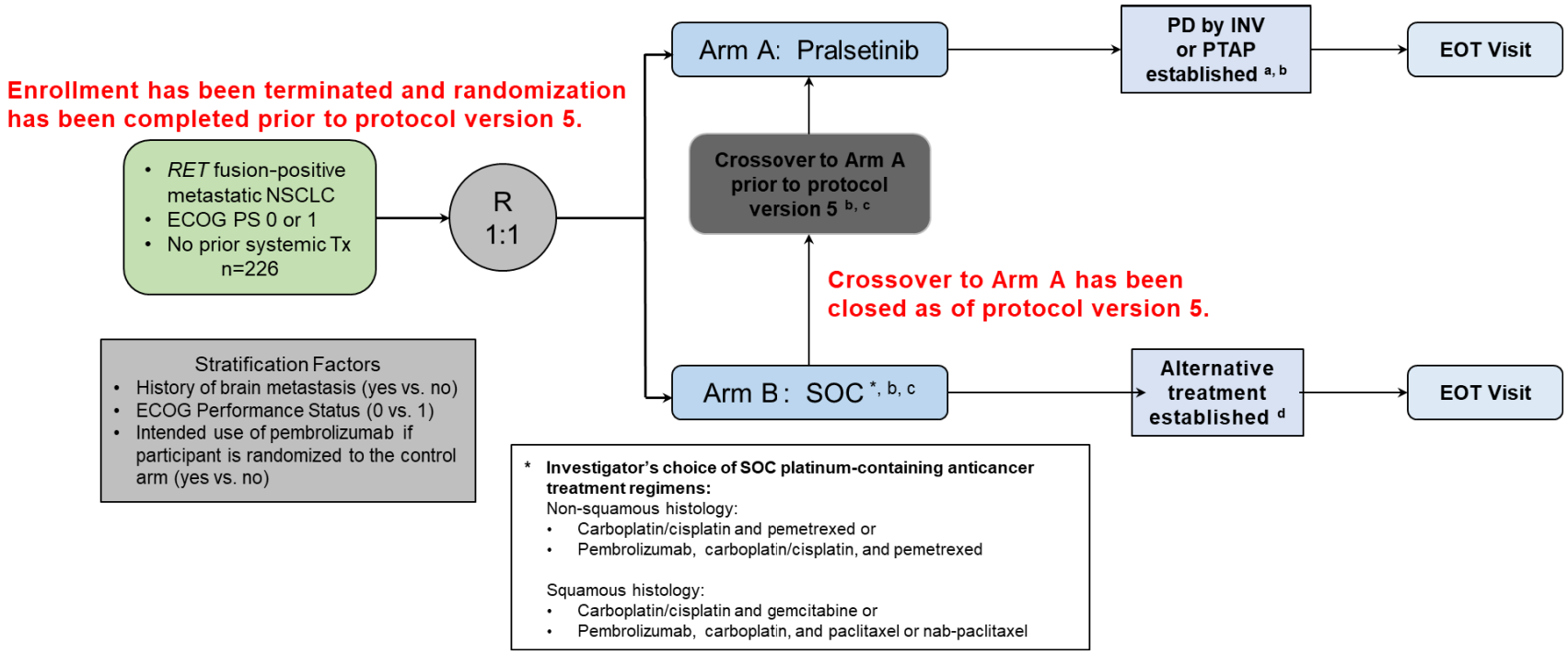
COMMITTEES

Independent Committees:	independent Data Monitoring Committee
Other Committees:	Not applicable

1.2 STUDY SCHEMA

The overall study design is presented in Figure 1.

Figure 1 Overall Study Design



ECOG PS = Eastern Cooperative Oncology Group Performance Status; EOT = end of treatment; INV = investigator; NSCLC = non-small cell lung cancer; PD = progressive disease; PTAP = Post-Trial Access Program; R = randomization; *RET* = rearranged during transfection; SOC = standard of care; tx = treatment.

[a] For participants randomized to Arm A, study treatment will be discontinued either at the time of PD as assessed by the investigator **or** at the time continued access solutions (PTAP) for pralsetinib is available, **or** when pralsetinib is no longer available, whichever comes first.

[b] For participants randomized to Arm B who crossed over to Arm A prior to protocol version 5, study treatment will be discontinued either at the time of PD as assessed by the investigator **or** at the time continued access solutions (PTAP) for pralsetinib is available, **or** when pralsetinib is no longer available, whichever comes first.

[c] Participants in Arm B no longer have the option to cross over to Arm A as of protocol version 5.

[d] Participants randomized to Arm B and still receiving SOC platinum-containing anticancer treatment at the time of protocol version 5 should be withdrawn from the study promptly. In the event that the SOC treatment regimen used within the study is not available to the participant after withdrawal, the participant may remain in the study and continue to receive the SOC treatment but must discontinue, at the latest, by the time the last patient receiving pralsetinib has discontinued from the study.

1.3 SCHEDULE OF ACTIVITIES AND SAMPLE COLLECTION SCHEDULES

Table 1 Schedule of Activities for Participants Randomized to Arm A and Participants Randomized to Arm B Who Did Not Crossover

		Treatment Period (3-Week Cycles)								EOT	
	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycles 7–17	Cycles 18 and Beyond [c]	Discon. Visit (EOT) [d]	Safety Follow-Up
Assessment or Procedure [a]	Days −28 to −1	Day 1 [b]	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Within 14 Days after Final Dose	Approx. 30 Days after Final Dose
Window (days)			±1	±4	±4	±4	±4	±4	±4		
Informed consent [f]	x										
Review of inclusion and exclusion criteria	x	x									
Demographics	x										
Medical history	x										
Prior medications and antineoplastic therapies	x										
Concomitant medications and procedures [g]		x	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x	x
Adverse events [i]	x	x	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x	x
Physical examination [j]	x	x	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x	
Vital signs	x	x	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x	

Table 1 Schedule of Activities for Participants Randomized to Arm A and Participants Randomized to Arm B Who Did Not Crossover (cont.)

	Screening	Treatment Period (3-Week Cycles)								EOT	
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycles 7–17	Cycles 18 and Beyond [c]	Discon. Visit (EOT) [d]	Safety Follow-Up
Assessment or Procedure [a]	Days −28 to −1	Day 1 [b]	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Within 14 Days after Final Dose	Approx. 30 Days after Final Dose
Window (days)			±1	±4	±4	±4	±4	±4	±4		
ECOG Performance Status	x	x	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x	
12-Lead ECG [k]	x	x				x [h]		x [h, k]	x [h, k]	x	
Tumor imaging [a, e] (including brain imaging)	x	As per local institutional standard of care.									
Serum or urine pregnancy test [l]	x [l]	x	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x	
Hematology [m]	x	x [n]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x	
Coagulation: PT, INR, and aPTT	x									x	
Serum chemistry panel [m]	x	x [n]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x [h]	x	
Serology: HBV, HCV, and HIV [o]	x										
Urinalysis	x	x [o]								x	

Table 1 Schedule of Activities for Participants Randomized to Arm A and Participants Randomized to Arm B Who Did Not Crossover (cont.)

		Treatment Period (3-Week Cycles)								EOT	
	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle4	Cycle 5	Cycle 6	Cycles 7–17	Cycles 18 and Beyond [c]	Discon. Visit (EOT) [d]	Safety Follow-Up
Assessment or Procedure [a]	Days −28 to −1	Day 1 [b]	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Within 14 Days after Final Dose	Approx. 30 Days after Final Dose
Window (days)			±1	±4	±4	±4	±4	±4	±4		
Tumor sample for central RET testing [p]	x										
TSH, free T3, and free T4 [q]	x			x [h]		x [h]		x [h]	x [h, q]	x	
Pralsetinib [r]		x (QD)									
Carboplatin or cisplatin [s]		x	x	x	x	x [u]	x [u]				
Gemcitabine [r]		x	x	x	x	x [u]	x [u]				
Pemetrexed [r]		x	x	x	x	x	x	x	x		
Pembrolizumab [r]		x	x	x	x	x	x	x	x		
Paclitaxel [r]		x	x	x	x	x [u]	x [u]				
Nab-paclitaxel [t]		x	x	x	x	x [u]	x [u]				
Survival and anti-cancer therapy follow-up										x	x

Table 1 Schedule of Activities for Participants Randomized to Arm A and Participants Randomized to Arm B Who Did Not Crossover (cont.)

CNS = central nervous system; Discon. = discontinuation; eCRF = electronic Case Report Form; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT4 = free thyroxin; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MN = mobile nursing; NA = not applicable; PET = positron emission tomography; PFS = progression-free survival; Q12W = every 12 weeks; QD = once a day; RET = rearranged during transfection; SOC = standard of care; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Every effort should be made to keep the scheduled assessments on time for each participant.

[a] In general, assessments and procedures are to be performed on Day 1 and before the first dose of study drug for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days). If treatment cycles are adjusted, all procedures except imaging will be completed according to the Cycle number and not weeks on treatment; imaging will be performed at the specified timepoints, regardless of treatment delays.

[b] Participants should receive their first dose of study treatment no later than 7 calendar days after randomization. After Day 1 of Cycle 1, each subsequent cycle may be delayed up to 28 days to allow for resolution of toxicities. Additional safety tests (e.g., hematology, chemistry, ECG) may be performed whenever clinically indicated, at the Investigator's discretion. Unless otherwise indicated, all tests and procedures must be performed predose at each visit. Whenever a test result is questionable, it should be repeated immediately.

[c] After Cycle 19 is completed, study visits can occur every two cycles (i.e., Cycles 21, 23, 25, etc.) per the investigator's discretion. Any additional monitoring necessary for chemotherapy management should be performed in accordance with SOC guidelines.

[d] To be completed within 14 days after the permanent discontinuation of study treatment and before a participant starts another anticancer therapy. EOT procedures do not need to be repeated if they were completed within 7 days.

[e] Imaging will be performed as per local institutional standard of care.

[f] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained up to 42 days (6 weeks) before randomization (refer to Section 8). Any participant who will undergo RET testing outside of current SOC should sign the Prescreening Informed Consent Form prior to acquisition of tumor sample.

[g] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment. Concomitant medications will be recorded on the Concomitant Medication eCRF from the time of signing informed consent to 30 days after the final dose. Note: Concomitant medications should also be recorded on Days 8 and 15 of Cycles 1–4 or 6 for participants receiving nab-paclitaxel and on Day 8 of Cycles 1–4 or 6 for participants receiving gemcitabine.

Table 1 Schedule of Activities for Participants Randomized to Arm A and Participants Randomized to Arm B Who Did Not Crossover (cont.)

[h] For participants at participating sites who have provided written informed consent to participate in MN visits, this assessment or procedure may be performed by a trained nursing professional at the participant's home or another suitable location in an appropriate setting. For participants in Arm A receiving pralsetinib, MN visits may be performed, starting on Day 1 of Cycle 2. For participants in Arm B, MN visits may be performed, starting on Day 1 of Cycle 4 or Cycle 6, or longer for participants receiving investigator's SOC choice of pemetrexed and pembrolizumab.

[i] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported (see Section 8.6.1). All adverse events will be reported from the start of treatment until 30 days after the final dose of study treatment. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 8.6.1 and Appendix 3). Note: Adverse events should also be reviewed on Days 8 and 15 of Cycles 1–4 or 6 for participants receiving nab-paclitaxel and on Day 8 of Cycles 1–4 or 6 for participants receiving gemcitabine.

[j] A complete physical examination will be performed at the screening visit, including height. Subsequent physical examinations will be disease and adverse events focused.

[k] Twelve-lead ECGs will be performed at screening, on Day 1 of Cycle 1, every 12 weeks thereafter, and at the EOT. QTc measurements will use the Fridericia's correction method. Other ECGs should be performed, if clinically indicated (for details, refer to Section 8.5.3).

[l] For all female participants of childbearing potential: A serum pregnancy test must be performed during screening within 7 days of starting Cycle 1. At subsequent timepoints, serum testing is preferred, but urine testing is allowed if a blood draw for other assessments is not performed. A serum or urine pregnancy test should be performed on Day 1 of each cycle after Day 1 of Cycle 1 and at the EOT. When study visits are less frequent than every 4 weeks, a local serum or urine pregnancy test has to be performed as required by local regulations (at least monthly). A positive urine test must be confirmed by a serum test.

[m] All blood samples should be collected predose, unless otherwise specified. Note: Hematology and serum chemistry panel should be performed on Days 8 and 15 of Cycles 1–4 for participants receiving nab-paclitaxel and on Day 8 for participants receiving gemcitabine.

[n] If the screening visit tests are performed within 7 days of Day 1 of Cycle 1, clinical laboratory tests do not need to be repeated on Day 1 of Cycle 1.

[o] Viral serology includes HIV, HBsAg, total HBcAb, and HCV antibody. HIV serology will be performed as per local standard after any applicable local consenting requirement is met. HBV serology includes HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA. If a participant has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the participant has an HBV infection, prior to randomization. HCV serology includes HCV antibody and (if HCV antibody test is positive) HCV RNA. If a participant has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

Table 1 Schedule of Activities for Participants Randomized to Arm A and Participants Randomized to Arm B Who Did Not Crossover(cont.)

[p] Tumor sample submitted for RET fusion status determination by central testing and assessment of other pathway biomarkers. If archived tumor tissue is not available, participants are required to undergo a pretreatment biopsy.

[q] Thyroid-stimulating hormone, free T3, and free T4 are to be checked every other cycle (i.e., every 6 weeks).

[r] Treatment regimen will be based on the treatment arm to which the participant is randomly assigned. If randomized to Arm B, specific SOC regimen will be based on investigator's choice, including dosing on Day 8 of the first 4 or 6 cycles, if regimen contains gemcitabine and Days 8 and 15 of Cycles 1-4 or 6 if the regimen contains nab-paclitaxel. See Section 6.1 for treatment details. Dispensing and accountability of study drug will also be performed at every visit for treatment regimen details.

[s] Each study site will administer chemotherapy for 4 or 6 cycles according to institutional guidelines. The selected chemotherapy agents should remain the same for all cycles (e.g., participants who start treatment with cisplatin should remain on cisplatin and not switch to carboplatin or vice versa and participants who start on paclitaxel should not switch to nab-paclitaxel). However, for participants who experience unacceptable toxicity with the selected chemotherapy, a switch may be considered. If a switch is considered due to toxicity, notify the Medical Monitor.

[t] Nab-paclitaxel dosing will occur on Days 1, 8, and 15, and gemcitabine dosing will occur on Days 1 and 8 of each cycle for up to 4 or 6 cycles. Note: Vital signs should be assessed on Days 8 and 15 of Cycles 1–4 or 6 for participants receiving nab-paclitaxel. See Section 6.1 for treatment details.

[u] SOC regimens can be administered up to 4 or 6 cycles based on local guidelines.

Table 2 Schedule of Activities for Participants Randomized to Arm B Who Crossed Over to Arm A

	Treatment Period (3-Week Cycles)								EOT	
	CC 1	CC 2	CC 3	CC 4	CC 5	CC 6	CCs 7–17	CCs 18 and Beyond [c]	Discon. Visit (EOT) [d]	Safety Follow-up
Assessment or Procedure [a]	Day 1 [b]	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Within 14 Days after Final Dose	Approx. 30 Days after Final Dose
Window (days)		±1	±4	±4	±4	±4	±4	±4		
Informed consent	x [f]									
Review of CC eligibility criteria [g]	x									
Concomitant medications and procedures [h]	x	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x	x
Adverse events [j]	x	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x	x
Physical examination [k]	x	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x	
Vital signs	x	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x	
ECOG Performance Status	x	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x	
12-Lead ECG [l]	x				x [h]		x [h, l]	x [h, l]	x	
Tumor imaging [a, e] (including brain imaging)	As per local institutional standard of care.									
Serum or urine pregnancy test [n]	x	x	x	x	x	x	x	x	x	
Hematology [o]	x [q]	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x	
Coagulation [o]: PT, INR, and aPTT	x [q]								x	
Serum chemistry panel [o]	x [q]	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x [i]	x	

Table 2 Schedule of Activities for Participants Randomized to Arm B Who Crossed Over to Arm A (cont.)

	Treatment Period (3-Week Cycles)								EOT	
	CC 1	CC 2	CC 3	CC 4	CC 5	CC 6	CCs 7–17	CCs 18 and Beyond [c]	Discon. Visit (EOT) [d]	Safety Follow-up
Assessment or Procedure [a]	Day 1 [b]	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Day 1	Within 14 Days after Final Dose	Approx. 30 Days after Final Dose
Window (days)		±1	±4	±4	±4	±4	±4	±4		
Urinalysis	x [p]								x	
TSH, free T3, and T4 [q]			x [i]		x [i]		x [i, q]	x [i, q]	x	
Pralsetinib [r]	x (QD)									
Survival and anticancer therapy follow-up									x	x

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

Every effort should be made to keep the scheduled assessments on time for each participant.

As of protocol version 5, participants are no longer eligible for crossover. Participants randomized to Arm B who experience progressive disease, as assessed by the investigator according to RECIST v1.1 and confirmed by BICR in the main treatment period, may be offered the opportunity to cross over and receive treatment with pralsetinib following up to at a 28-day washout period after their last dose of investigator's choice of SOC platinum-containing anticancer treatment regimen in Arm B. Separate informed consent for participants will be required at the time of progression, as confirmed by the BICR, for the participant to be eligible for crossover.

[a] In general, assessments and procedures are to be performed on Day 1 and prior to the first dose of study drug for each cycle unless otherwise specified and not weeks on treatment. Imaging will be performed at the specified timepoints, regardless of treatment delays.

[b] After Day 1 of CC 1, each subsequent cycle may be delayed up to 28 days to allow for resolution of toxicities. Additional safety tests (e.g., hematology, chemistry, and ECG) may be performed whenever clinically indicated at the investigator's discretion. Unless otherwise indicated, all tests and procedures may be performed predose at each visit. Whenever a test result is questionable, it should be repeated immediately.

[c] After CC 19, study visits can occur every two cycles (i.e., CCs 21, 23, 25, etc.) per the investigator's discretion.

[d] If an alternate treatment is started within 14 days of the last dose of study drug, the EOT visit should be conducted before the first dose of alternate therapy. EOT procedures do not need to be repeated if they are completed within 7 days (or within 28 days for disease response assessments).

Table 2 Schedule of Activities for Participants Randomized to Arm B Who Crossed Over to Arm A (cont.)

[e] Imaging will be performed as per standard of care.

[f] Participants must provide signed informed consent for crossover to praseltinib treatment prior to starting pralsetinib.

[g] See Section 5.3 for a detailed explanation of the eligibility criteria and procedures for crossing over from Arm B to receive pralsetinib.

[h] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment. Concomitant medications will be recorded on the Prior and Concomitant Medication and Therapies eCRF.

[i] For participants at participating sites who have provided written informed consent to participate in MN visits, this assessment or procedure may be performed by a trained nursing professional at the participant's home or another suitable location in an appropriate. Participants during the CC treatment period, MN visits may be performed, starting on Day 1 of CC 2.

[j] After initiation of crossover study treatment, all adverse events will be reported until 30 days after the final dose of study treatment (see Section 8.6.1). After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Appendix 3). Any adverse events that were ongoing from Arm A and worsened in crossover should be recorded as a new adverse event in the Adverse Event eCRF with the onset date and severity reported from the onset of the worsening (see Section 8.6.3 and Appendix 3, Section A3–4.1).

[k] A complete physical examination will be performed at the Day 1, CC 1 visit, including height. Subsequent physical examinations will be disease and adverse event focused.

[l] A single 12-lead ECG will be performed at screening, on Day 1 of CC 1, and every 12 weeks thereafter, and at the EOT. Subsequently, ECG should be repeated if clinically indicated.

[n] To be performed for female participants of childbearing potential. At subsequent timepoints, serum testing is preferred, but urine testing is allowed if a blood draw for other assessments is not performed. A serum pregnancy test should be performed on Day 1 CC 1 (within 7 days before Day 1 of CC 1). A serum or urine pregnancy test should be performed starting on Day 1 of each cycle after Day 1 of CCs 1 and at the EOT. When study visits are less frequent than every 3 weeks, a local serum or urine pregnancy test may be performed as required by local regulations (at least once every month). A positive urine test must be confirmed by a serum test.

[o] All blood samples should be collected predose unless otherwise specified.

[p] If the clinical laboratory tests are performed within 7 days of Day 1 of CC 1, they do not need to be repeated on Day 1 of CC 1.

[q] Thyroid-stimulating hormone, free T3, and T4 are to be checked every other cycle (i.e., every 6 weeks).

[r] See Section 6.1 for treatment details. Dispensing and accountability of pralsetinib will also be performed at every visit for treatment regimen details.

2. INTRODUCTION

2.1 STUDY RATIONALE

During the last two decades, the evolution of genetic testing has resulted in the identification of genetic alterations that play key roles as oncogenic drivers in lung cancer, leading to the development of targeted therapies and immunotherapies to treat patients in an individualized way (Rosell and Karachaliou 2016). For patients with tumors harboring specific oncogenic drivers, such as EGFR, ALK, ROS1, and BRAF, targeted kinase inhibitor therapies have resulted in significantly higher overall survival (OS) compared with patients treated with conventional therapies (Barlesi et al. 2016; Rosell and Karachaliou 2016). Oncogenic rearranged during transfection (RET) fusions have been identified in 1%–2% of patients with non-small cell cancer (NSCLC). However, despite the clear role of RET as an oncogenic driver, owing to the lack of globally approved and available therapies targeting RET, diagnostic testing for RET is not standard of care (SOC), and patients with RET fusion–positive advanced NSCLC are treated per guidelines (National Institute for Health and Care Excellence [NICE] 2019; National Comprehensive Cancer Network® [NCCN®] 2020; Planchard et al. 2020) adenocarcinoma and squamous cell carcinoma that is negative for actionable molecular markers. Standard treatment for patients with advanced, non-resectable NSCLC lacking a driver mutation is cytotoxic chemotherapy and immunotherapy with a checkpoint inhibitor. Cytotoxic chemotherapy generally has a response rate of approximately 30%–40% in the first-line setting (using platinum-based combinations) and approximately 10% in the second-line setting (Ardizzoni et al. 2007; Herbst et al. 2018). Recent data indicate that patients with NSCLC carrying an oncogenic driver mutation are typically not responsive to checkpoint inhibitors (Mazieres et al. 2018; Sabari et al. 2018; Tufman et al. 2018). This low immunotherapy response rate is seen despite expression of programmed death–ligand 1 (PD-L1) in a substantial portion of the RET fusion–positive lung cancers and may be attributed to the overall lower tumor mutation burden in RET fusion–positive lung cancers compared with lung cancers that do not have activation of a dominant driver such as RET (Mazieres et al. 2018; Sabari et al. 2018; Tufman et al. 2018).

Pralsetinib is a potent and selective inhibitor of oncogenic RET alterations. Based on the promising results from the ARROW trial of pralsetinib in previously treated patients with advanced NSCLC, the potential for pralsetinib to offer a more effective treatment with improved tolerability than current SOC therapies in the RET-driven NSCLC population and the modest overall clinical benefit of standard first-line therapy for patients with RET-dependent NSCLC, novel approaches directly targeting RET are necessary for patients with advanced NSCLC in the first-line setting.

The purpose of this study is to assess the efficacy and safety of pralsetinib compared with SOC for the first-line treatment of patients with RET fusion–positive, metastatic NSCLC. SOC treatment will be investigator's choice of SOC platinum-containing anticancer treatment regimens, as measured primarily by progression-free survival

(PFS), for patients with RET fusion–positive metastatic NSCLC who have not previously received treatment with a multikinase inhibitor (MKI) for metastatic disease.

2.2 BACKGROUND

Pralsetinib (formerly known as BLU-667) is a potent and selective inhibitor of oncogenic *RET* alterations. The *RET* receptor tyrosine kinase is expressed in several neural, neuroendocrine, and genitourinary tissue types that normally require ligand and co-receptor binding for activation. Oncogenic *RET* rearrangements have been identified in 1%–2% of NSCLC (Lin et al. 2015). The rearrangements typically produce chimeric transcripts that encode a fusion protein consisting of the *RET* kinase domain coupled to a protein with a dimerization domain (e.g., KIF5B, CCDC6, NCOA4), resulting in a constitutively active kinase that promotes tumorigenesis.

In the ongoing first-in-human study of pralsetinib (ARROW; BLU-667-1101), a preliminary response rate of 58% to pralsetinib monotherapy was observed in patients with advanced NSCLC bearing *RET* fusions as the sole oncogenic driver, and pralsetinib monotherapy has been generally well tolerated at doses up to 400 mg once a day (QD) (Gainor et al. 2019).

Lung cancer is the leading cause of cancer-related death worldwide, with an estimated 2.1 million new cases and 1.8 million deaths in 2018 (WHO 2018). Lung cancer has two main subtypes, small-cell lung cancer and NSCLC, with approximately 85% of patients falling into the histologic subtype of NSCLC. NSCLCs are generally subcategorized into adenocarcinoma, squamous cell carcinoma, and large cell (undifferentiated) carcinoma.

Oncogenic *RET* fusions have been identified in 1%–2% of NSCLC (Lipson et al. 2012; Takeuchi et al. 2012; Stransky et al. 2014). RET fusions are typically found in adenocarcinoma histology (although occasionally squamous) and tend to occur more frequently in young patients who are not smokers. Owing to the lack of available therapies targeting RET, diagnostic testing for RET is not SOC, and patients with RET fusion–positive advanced NSCLC are treated per NCCN and European Society of Medical Oncology (ESMO) guidelines (NCCN 2020; Planchard et al. 2020) for actionable molecular marker–negative adenocarcinoma and squamous cell carcinoma. Standard treatment for patients with advanced, non-resectable NSCLC lacking a driver mutation is cytotoxic chemotherapy and immunotherapy with checkpoint inhibitor. Subsequent therapy for patients whose disease is refractory to treatment consists of best supportive care additional cytotoxic chemotherapy or enrollment in a clinical trial.

Platinum-based chemotherapy regimens remain the mainstay of first-line therapy globally for patients with advanced NSCLC with no actionable oncogenic mutations. The addition of bevacizumab has also shown benefit for patients with adenocarcinoma, including patients with NSCLC, but is associated with a greater incidence of bleeding events and treatment-related deaths. Immune checkpoint inhibition, either as monotherapy or in combination with platinum-based chemotherapy, with or without

bevacizumab, is also an option for patients lacking actionable oncogenic mutations. However, the presence of an oncogenic mutation is associated with low PD-L1 expression and is predictive of a lack of benefit of single-agent checkpoint inhibitor therapy (Mazieres et al. 2018).

Detailed information on pralsetinib is provided in the Pralsetinib Investigator's Brochure.

2.3 PRALSETINIB

Pralsetinib (formerly known as BLU-667) is a potent and selective inhibitor of RET fusion proteins and oncogenic *RET* mutants.

2.3.1 Nonclinical Activity

Preclinical Pharmacology

A summary of nonclinical information is provided in the Pralsetinib Investigator's Brochure. Key pharmacokinetic (PK) drug–drug interactions (DDIs) in the pralsetinib clinical program, based on recently completed studies, are presented below.

In vitro studies demonstrated that the Phase I metabolism of pralsetinib is primarily mediated by CYP3A4, with minor contribution from CYP2D6 and CYP1A2, whereas glucuronidation is primarily catalyzed by UGT1A4. Pralsetinib is also a P-glycoprotein (P-gp) substrate. Therefore, strong CYP3A and/or P-gp inhibitors and inducers may affect circulating levels of pralsetinib.

In vitro, pralsetinib is a reversible inhibitor of CYP2C8, CYP2C9, and CYP3A4 (testosterone 6β-hydroxylation) with K_i values of 9.6, 4.1, and 24 μM, respectively. Pralsetinib also demonstrated time-dependent inhibition of CYP3A4 (testosterone 6β-hydroxylation) in vitro with a K_{inact} and K_I of 0.24 min-1 and 154 μM, respectively. The R1 values for CYP2C8, CYP2C9, and CYP3A4 inhibition, $R1_{gut}$, and R2 value for CYP3A4 inhibition for pralsetinib are either at or above the threshold for a potential clinical DDI (i.e., $R1 \geq 1.02$, $R1_{gut} > 11$, and $R2 \geq 1.25$). Therefore, clinical DDIs with concomitant medications for which CYP2C8-, CYP2C9-, or CYP3A-mediated metabolism constitute the primary mechanism of clearance are likely.

In vitro in human hepatocytes, pralsetinib (0.03 to 10 μM) was a weak inducer of CYP1A2 with a maximal induction of 2.0-fold (< 1% of positive control response), 2.7-fold (1% of positive control response), and 2.6-fold (2% of positive control response) in Lots 336, 348B, and 412, respectively. Pralsetinib caused concentration-dependent induction of CYP2B6 mRNA expression in two lots with a maximal induction of 4.1-fold (35% of positive control response) and 3.5-fold (26% of positive control response) in Lots 336 and 412, respectively. Pralsetinib 50% effective concentration (EC50) and maximum effective concentration (E_{max}) for CYP2B6 induction (based on mRNA expression) were estimated as 0.22 μM and 3.6-fold, and 0.36 μM and 3.7-fold in Lot 336 and Lot 412, respectively. Pralsetinib caused concentration-dependent induction of CYP3A4 mRNA expression in all three lots tested with a maximal induction

of 9.6-fold (37% of positive control response), 3.7-fold (30% of positive control response), and 7.3-fold (74% of positive control response) in Lots 336, 348B, and 412, respectively. Pralsetinib EC_{50} and E_{max} for CYP3A4 induction (based on mRNA expression) were estimated as 1.4 μM and 8.7-fold, and 3.0 μM and 3.7-fold in Lots 336 and 348B, respectively. Pralsetinib EC_{50} and E_{max} for CYP3A4 induction (based on enzyme activity levels) were estimated as 0.35 μM and 3.2-fold in Lot 336.
The estimated R3 value is ≤0.8, the threshold for a potential clinical DDI. Given that activation of the pregnane X receptor results in co-induction of CYP3A and CYP2C enzymes, DDIs with comedications that are predominantly metabolized by these enzymes are likely.

Pralsetinib is a dual P-gp/BCRP substrate but is not a substrate of OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, BSEP, MATE1, or MATE2-K. Results from in vitro studies indicate that at clinically relevant concentrations, pralsetinib is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K. Therefore, pralsetinib may have the potential for PK drug interactions with substrates of these transporters. Pralsetinib at clinically relevant concentrations did not significantly inhibit OAT3, OCT1, OCT2, or BSEP transport activity and the likelihood for a clinical DDI is low.

2.3.2 Clinical Experience

The pralsetinib clinical development program was initiated in November 2016 and includes two ongoing clinical study in patients.

- Study BLU-667-1101 ("ARROW") is a Phase I/II study of the highly selective RET inhibitor, pralsetinib, in patients with medullary thyroid cancer (MTC), NSCLC, and other advanced solid tumors.
- Study BO41932 (Tapistry) is a Phase II tumor agnostic precision immune-oncology platform trial

The Phase II portion of the ARROW study recruited patients at the recommended Phase II dose (RP2D) of 400 mg QD.

Safety

Overall, in the ARROW study, treatment at dose levels ≤400 mg, including the RP2D of 400 mg orally (PO) QD, has demonstrated acceptable tolerability, with most adverse events being of low grade and reversible. All adverse events that have occurred in ≥ 15% of all patients (n=528) treated at 400 mg QD dose level, as of the data cutoff date of 6 November 2020, including their severity and relatedness, are listed in Table 3.

As of 6 November 2020, across the entire study, 6.3% of patients have discontinued treatment because of treatment-related toxicity. Of the patients with NSCLC treated at a starting dose of 400 mg QD (n=281), a total of 7.5% of patients discontinued pralsetinib because of the following treatment-related toxicities, as follows: pneumonitis (7 patients; 2.5%): pneumonia or thrombocytopenia (2 patients each; <1%); anemia, blood creatine

phosphokinase increased, chest pain, colitis, constipation, electrolyte imbalance, fatigue, gait disturbance, hyponatremia, hypoxia, lymphocyte count decreased, neutropenia, pancytopenia, respiratory distress, rhabdomyolysis, or stomatitis (1 patient each; $<1\%$). Additional details are provided in Pralsetinib Investigator's Brochure.

Table 3 Adverse Events and Treatment-Related Adverse Events Experienced by 15% of All Patients (n=528) Treated at 400 mg QD, in the ARROW (BLU-667-1101) Study

	Adverse Events with Overall Rate $\geq 15\%$		Treatment-Related Adverse Events Amongst Ones with Overall Rate $\geq 15\%$ [a]		
Adverse Event	All	Grade ≥ 3	All	Grade 3	Grade 4
AST increased	243 (46.0)	30 (5.7)	206 (39.0)	12 (2.3)	2 (<1)
Anemia	241 (45.6)	91 (17.2)	179 (33.9)	64 (12.1)	0
Constipation	221 (41.9)	3 (<1)	142 (26.9)	3 (<1)	0
ALT increased	179 (33.9)	22 (4.2)	152 (28.8)	10 (1.9)	1 (<1)
Hypertension	172 (32.6)	85 (16.1)	133 (25.2)	64 (12.1)	0
Diarrhea	155 (29.4)	15 (2.8)	79 (15.0)	6 (1.1)	0
WBC count decreased	142 (26.9)	32 (6.1)	133 (25.2)	28 (5.3)	1 (<1)
Pyrexia	133 (25.2)	6 (1.1)	24 (4.5)	0	0
Fatigue	132 (25.0)	12 (2.3)	81 (15.3)	8 (1.5)	0
Neutrophil count decreased	128 (24.2)	51 (9.7)	120 (22.7)	43 (8.1)	5 (<1)
Blood creatinine increased	118 (22.3)	2 (<1)	76 (14.4)	1 (<1)	0
Neutropenia	116 (22.0)	59 (11.2)	109 (20.6)	46 (8.7)	9 (1.7)
Cough	114 (21.6)	3 (<1)	18 (3.4)	2 (<1)	0
Hypocalcemia	109 (20.6)	19 (3.6)	49 (9.3)	5 (<1)	2 (<1)
Hyperphosphatemia	94 (17.8)	1 (<1)	86 (16.3)	0	0
Dyspnea	89 (16.9)	13 (2.5)	10 (1.9)	1 (<1)	0
Blood CPK increased	86 (16.3)	34 (6.4)	81 (15.3)	24 (4.5)	8 (1.5)
Dry mouth	84 (15.9)	0	63 (11.9)	0	0
Nausea	84 (15.9)	1 (<1)	37 (7.0)	0	0
Headache	82 (15.5)	2 (<1)	26 (4.9)	1 (<1)	0
Edema peripheral	82 (15.5)	1 (<1)	35 (6.6)	0	0
Dysgeusia	81 (15.3)	0	69 (13.1)	0	0
Decreased appetite	80 (15.2)	5 (<1)	34 (6.4)	1 (<1)	0

CPK = creatine phosphokinase; QD = once a day.

[a] No patient experienced a Grade 5 adverse reaction with an overall reporting rate $\geq 15\%$.
Data cutoff date: 6 November 2019

Efficacy

As presented at the American Society of Clinical Oncology (ASCO) in 2021 and shown in Figure 2, pralsetinib demonstrates broad and durable antitumor activity in patients with RET fusion-positive NSCLC, regardless of treatment history, RET fusion partner or mutation, or central nervous system (CNS) involvement. The objective response rate (ORR) was 62% with 91% disease control rate (DCR) in patients with NSCLC previously treated with platinum chemotherapy. In treatment-naive patients with RET fusion–positive NSCLC ORR was 79% (Curigliano et al. 2021).

Figure 2 Efficacy Summary (Blinded Independent Central Review)

Efficacy summary (blinded independent central review)

	Measurable disease population					
	RET fusion–positive NSCLC (n=216)	Treatment-naïve			Prior treatment	
		All (n=68)	Pre-eligibility revision (n=43)[a]	Post eligibility revision (n=25)[a]	Prior platinum (n=126)	Prior non-platinum (n=22)
ORR, % (95% CI)	**69** (62–75)	**79** (68–88)	**74** (59–87)	**88** (69–98)	**62** (53–70)	**73** (50–89)
Best overall response, n (%)						
CR	9 (4)	4 (6)	4 (9)	0	5 (4)	0
PR	139 (64)	50 (74)	28 (65)	22 (88)	73 (58)	16 (73)
SD	50 (23)	9 (13)	7 (16)	2 (8)	37 (29)	4 (18)
PD	10 (5)	3 (4)	3 (7)	0	5 (4)	2 (9)
NE	8 (4)	2 (3)	1 (2)	1 (4)	6 (5)	0
DCR, % (95% CI)[b]	92 (87–95)	93 (84–98)	91 (78–97)	96 (80–100)	91 (85–96)	91 (71–99)
CBR, % (95% CI)[c]	77 (71–82)	82 (71–91)	79 (64–90)	88 (69–98)	74 (65–81)	77 (55–92)
mDOR, mo (95% CI)	22.3 (15.1–NR)	NR (9.0–NR)	11.0 (7.4–NR)	NR (NR–NR)	22.3 (15.1–NR)	NR (9.2–NR)
mPFS, mo (95% CI)[d]	16.4 (11.0–24.1) n=233	13.0 (9.1–NR) n=75	10.9 (7.7–NR) n=47	NR (NR–NR) n=28	16.5 (10.5–24.1) n=136	12.8 (9.1–NR) n=22

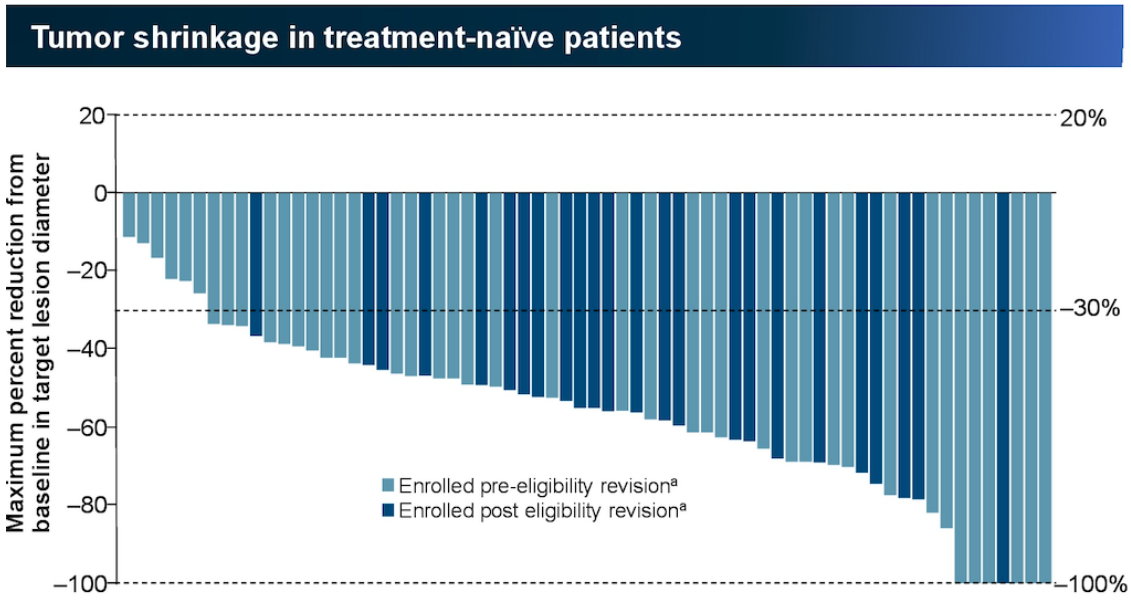
CBR = clinical benefit rate; CR = complete response; DCR = disease control rate; ECOG PS = Eastern Cooperative Oncology Group performance status; mDOR = median duration of response; mPFS = median progression-free survival; NE = not evaluable; PD = progressive disease; ORR = overall response rate; PR = partial response; SD = stable disease.

[a] Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naive patients eligible for standard platinum-based therapy who had previously not been permitted.

[b] ECOG PS of 2 was permitted prior to protocol amendment in July 2018.

[c] History of or current ECOG performance status.

Figure 3 Tumor Shrinkage in Treatment-Naive Patients



[a] Protocol amendment July 2019; this amendment expanded inclusion criteria to allow recruitment of treatment-naive patients eligible for standard platinum-based therapy who had previously not been permitted.

2.4 BENEFIT–RISK ASSESSMENT

To date, pralsetinib has demonstrated broad and durable anti-tumor activity in patients with RET fusion–positive NSCLC and RET-mutated MTC, regardless of treatment history, RET fusion partner or mutation, or CNS involvement. The ORR of pralsetinib in these unmet need populations ranged from 58% up to 83% depending on the indication. The overall safety experience suggests that pralsetinib has a favorable tolerability profile in patients with advanced cancer and that most adverse events and serious adverse events are readily detected and managed with current safety monitoring procedures. Taken together, the available information indicates that the benefit–risk ratio for pralsetinib therapy is acceptable for further development and justifies studying pralsetinib in a randomized protocol setting to potentially replace the existing SOC.

Refer to Appendix 5 for information on the anticipated risks during pralsetinib administration and risk mitigation measures, including guidelines for managing adverse events associated with pralsetinib.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of pralsetinib may be found in the Pralsetinib Investigator's Brochure.

2.5 COVID-19 BENEFIT-RISK ASSESSMENT

In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are a more vulnerable population. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with higher morbidity and mortality in patients with cancer in some retrospective analyses. It is unclear whether or how cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, affect the incidence or severity of COVID-19. It is not known whether any of the agents being investigated in this study will increase the risk of infection with SARS-CoV-2. Participants with a serious infection requiring IV antibiotics within 7 days prior to initiation of study treatment or any active infection that, in the opinion of the investigator, could impact patient safety will be excluded from study participation, and participants will be carefully monitored for infections during the study.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with pralsetinib and clinical and radiologic features for SARSCoV-2 related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

2.6 COVID-19 VACCINES

Based on a specific benefit-risk assessment, taking into account the available relevant information, the approved non-live COVID-19 vaccines should be administered in patients who are in the study, as long as there is no other contraindication (e.g., known hypersensitivity to a vaccine component).

Although there is no specific requirement regarding the timing of vaccine administration, the vaccination should ideally be at least commenced before study enrollment and initiation of study drug, whenever possible.

Details of any COVID-19 vaccination received before study enrollment should be captured in the medical history section, at screening, whereas details regarding the COVID-19 vaccine received during the study should be recorded in the concomitant medication section.

Investigators should share with patients' primary healthcare providers relevant information regarding any potential effect of respective study drugs on the response to COVID-19 vaccination, as applicable. Also, patients should contact the investigators or site staff, when they are invited to receive a COVID-19 vaccine deployed in their region.

The decision to vaccinate a patient should be based on a patient’s SARS-CoV-2 infection/complication risk, general health condition, severity of underlying malignancy, and regional epidemiology of COVID-19. COVID-19 vaccines should be administered in accordance with their respective prescribing information and applicable immunization guidelines.

After COVID-19 vaccination, one should continue to observe the applicable epidemiologic/public health and hygiene measures during the pandemic, along with per protocol safety measures and assessments in order to minimize the risk and to appropriately identify and assess potential adverse reactions (e.g., nausea, diarrhea, myalgia) possibly shared by vaccines and study drugs.

Based on the published mechanism of action of the COVID-19 vaccines and the known mechanism of action of pralsetinib, there is no scientific rationale to expect that COVID-19 vaccines will affect the efficacy of pralsetinib.

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of pralsetinib compared with investigator's choice of SOC platinum-containing anticancer treatment regimens (for a description of the SOC anticancer treatment regimens, see Section 4.1.1) in participants with RET fusion-positive NSCLC who have not previously received treatment in the metastatic setting. Specific objectives and corresponding endpoints for the study are presented in Table 4.

Table 4 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To assess whether pralsetinib improves PFS compared with investigator's choice of SOC platinum-containing anticancer treatment regimens for participants with RET fusion–positive metastatic NSCLC	• PFS, defined as the time from randomization date to the first documented PD, as assessed by investigator according to RECIST v1.1 or death due to any cause, whichever occurs first
Key Secondary Objectives	**Key Corresponding Endpoints**
• To evaluate the efficacy of pralsetinib compared with compared with investigator's choice of SOC platinum-containing anticancer treatment regimens	• ORR, defined as the proportion of participants with a CR or a PR on two consecutive occasions ≥4 weeks apart, as assessed by investigator according to RECIST v1.1
• To evaluate OS	• OS, defined as the time from randomization date to death due to any cause
Additional Secondary Objectives	**Additional Corresponding Endpoints**
• To evaluate the safety and tolerability of pralsetinib compared with investigator's choice of SOC platinum-containing anticancer treatment regimens	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 • Change from baseline ECOG Performance Status • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results

Table 4 Objectives and Corresponding Endpoints (cont.)

Additional Secondary Objectives (cont.)	Additional Corresponding Endpoint(s) (cont.)
• To compare additional measures of anticancer activity	• DOR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), as assessed by investigator according to RECIST v1.1 • CBR, defined as the proportion of participants who experience a best response of SD with a minimum duration of 6 months, a CR, or a PR, as assessed by investigator according to RECIST v1.1 • DCR, defined as the proportion of participants who experience a best response of CR, or PR, or SD, as assessed by investigator according to RECIST v1.1

CBR = clinical benefit rate; CR = complete response; CTCAE v5.0 = Common Terminology Criteria for Adverse Events, Version 5.0; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; NCI = National Cancer Institute; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RET = rearranged during transfection (oncogene); SD = stable disease; SOC = standard of care.

4. STUDY DESIGN

Following the Sponsor's decision to prematurely terminate the study, participants randomized to Arm A and participants in Arm B who crossed over to Arm A should continue to receive study treatment and undergo the revised study assessments as indicated in the schedule of activities (Section 1.3) and described in Section 8 until study discontinuation.

Participants randomized to Arm B and still receiving SOC platinum-containing anticancer treatment at the time of protocol version 5 should be withdrawn from the study promptly. In the event that the SOC treatment regimen used within the study is not available to the participant after withdrawal, the participant may remain in the study and continue to receive the SOC treatment but must discontinue, at the latest, by the time the last patient receiving pralsetinib has discontinued from the study. Investigators will be given advanced notice of this timepoint. Crossover from Arm B (SOC) to Arm A will no longer be an option.

The study will be closed once all patients receiving pralsetinib have left the study or pralsetinib is no longer available, whichever occurs first.

4.1 OVERALL DESIGN

This is a Phase III, randomized, open-label, two-arm, international study designed to evaluate the efficacy and safety of pralsetinib compared with platinum chemotherapy-based regimen chosen by the investigator from a list of SOC platinum-containing anticancer treatment regimens. PFS, as assessed by investigator, is the primary endpoint for patients with RET fusion–positive metastatic NSCLC who have not previously received a systemic anticancer therapy for metastatic disease.

The study is divided into two periods: a screening period (of up to 28 days in length)and a treatment period of variable duration (as indicated by tolerance and disease status). Safety follow-up assessment will occur approximately 30 days after the final dose of study drug.

All study visits are intended to be conducted on an outpatient basis but may be conducted on an inpatient basis, as needed. Informed consent may be obtained up to 42 days (6 weeks) before study drug administration on Day 1 of Cycle 1. After informed consent, participants will be evaluated for study eligibility during the screening period, which is to be completed within 28 or fewer days before randomization. For study eligibility, RET fusion status may be determined locally or centrally. However, baseline tumor tissue samples for all participants must also be submitted for confirmation of RET fusion status by central testing.

After the screening assessments are performed, participants will be randomly assigned in a 1:1 ratio to one of two treatment arms: Arm A (pralsetinib) or Arm B (investigator's choice of platinum-containing anticancer treatment regimen selected from a list of SOC regimens, with or without pembrolizumab; refer to Section 4.1.1 for description), stratified by history of brain metastasis (yes vs. no), Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1), and intended use of pembrolizumab if randomized to the control arm (yes vs. no).

4.1.1 Main Treatment Period

During the main treatment period, participants randomized to Arm A will receive pralsetinib at a dose of 400 mg QD PO in continuous 21-day treatment cycles. Participants may continue to receive pralsetinib until disease progression as assessed by the investigator, until continued access solutions for pralsetinib are available, when pralsetnib is no longer available, or precluded by toxicity, non-compliance, withdrawal of consent, death, or closure of the study by the Sponsor (see Section 7.2), whichever comes first.

Participants randomized to Arm B will receive one of the following SOC platinum-containing anticancer treatment regimens, as determined by the treating investigator:

- For participants with NSCLC of non-squamous histology
  - Carboplatin or cisplatin and pemetrexed (with vitamin supplementation); with optional pemetrexed (with vitamin supplementation) maintenance
  - Pembrolizumab in combination with carboplatin or cisplatin in combination pemetrexed (with vitamin supplementation), followed by pembrolizumab and optional pemetrexed (with vitamin supplementation) maintenance
- For participants with NSCLC of squamous histology
  - Carboplatin or cisplatin and gemcitabine
  - Pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel

Investigator's choice of platinum-containing anticancer treatment regimen may continue in accordance with SOC (four or six 3-week treatment cycles according to institutional guidelines). Participants with NSCLC of non-squamous histology receiving carboplatin- or cisplatin-containing regimens may optionally receive subsequent maintenance treatment with pemetrexed (and pembrolizumab, if selected). Participants with NSCLC of squamous histology receiving carboplatin and paclitaxel-containing regimens may optionally receive maintenance treatment with pembrolizumab, if selected. Pembrolizumab and/or pemetrexed maintenance therapy can be continued for up to 2 years unless stopped earlier owing to toxicity, confirmed disease progression, non-compliance, withdrawal of consent, death, or closure of the study by the Sponsor (see Section 7.2). As of protocol version 5, participants receiving SOC platinum-containing anticancer treatment should be withdrawn from the study promptly. In the event that the SOC treatment regimen used within the study is not available to the participant after withdrawal, the participant may remain in the study and continue to receive the SOC treatment but must discontinue, at the latest, by the time the last patient receiving pralsetinib has discontinued from the study. Investigators will be given advanced notice of this timepoint.

All participants will present to the study center on Day 1 of Cycle 1 for the first dose of study drug, safety monitoring (including ECOG Performance Status assessment, physical examination, vital signs, ECG, safety laboratory tests, adverse event, and concomitant medication recording, etc.), quality-of-life (QoL) questionnaires, biomarker sample collection, and PK assessments. Additional study visits for assessment of safety will be conducted periodically throughout study treatment in accordance with the schedule of activities (see Section 1.3, Table 1 and Table 2).

4.1.2 Crossover Treatment Period

Following the Sponsor's decision to prematurely terminate the study , the option for participants in Arm B (SOC) to crossover to Arm A (pralsetinib) was removed as of

protocol version 5. Participants who have already crossed over will follow the assessments as indicated in the schedule of activities (Section 1.3, Table 2).

4.1.3 End of Treatment Period and 30-Day Follow-Up Contact

All participants will attend an end of treatment (EOT) visit within 14 days after the final dose of study drug. The EOT visit should be conducted before the participant starts an antineoplastic therapy. The EOT procedures do not need to be repeated if they are completed within 7 days (or within 28 days for disease response assessments) prior to the final dose. Safety follow-up assessment will occur approximately 30 days after the final dose of study drug or initiates an antineoplastic therapy.

4.1.4 Follow-Up Period

Following the announcement of premature study termination, data on long-term PFS, OS, and new anti-cancer therapies will no longer be collected. However, the safety follow-up assessment described in Section 4.1.3 is required.

4.1.5 Independent Data Monitoring Committee

A formal independent Data Monitoring Committee (iDMC) will be formed for this study. The aim of the iDMC is to safeguard the interests of trial participants, monitor the main outcome measures, including safety and efficacy, and the overall conduct of the trial.

The role of iDMC is to perform periodic review of the study's progress, including adherence to protocol, follow-up assessments, and safety data. The iDMC will receive information on the progress and data accumulation in this study and provide advice on the study conduct. The iDMC will also make any necessary recommendations to the Sponsor relevant to the study design.

The iDMC will perform reviews of unblinded safety data until the Sponsor is unblinded, after which the study team will be responsible for the ongoing monitoring of patient safety in the study.

Further details, including membership and specific roles and responsibilities of the iDMC, will be described separately in the iDMC Charter.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

Targeted therapy has helped improve the care of patients with lung cancer with a specific molecular driver. Novel targeted therapies have demonstrated robust response rates and PFS. For example, in the case of EGFR-targeted therapy, an improvement in OS has recently been reported with a third generation TKI (Ramalingam et al. 2020). Similarly, for patients with ALK gene rearrangement, second-generation ALK inhibitors are associated with a median PFS of longer than 2 years (Peters et al. 2017).

Such agents are also associated with marked anticancer activity against brain metastasis, which is common in these molecular subsets of NSCLC.

RET gene fusions are present in approximately 1%–2% of NSCLC. RET is emerging as a new targetable driver for this population. Despite sensitivity to platinum-based chemotherapy and conflicting small reports regarding the limited efficacy of immune checkpoint inhibitor (Mazieres et al. 2019), there have been limited treatment approaches for this subset of patients. Multiple non-selective RET TKIs exhibited modest anti-RET activity with an increased off-target toxicity profile that often required dose interruption, reduction, or treatment cessation (Lee et al. 2017; Hida et al. 2019). The increased toxicity is because of stronger inhibition of other targets, such as VEGFR and EGFR inhibition, and an unfavorable PK profile for use in this setting.

Platinum-based chemotherapy combinations are the current SOC for the first-line treatment of metastatic RET fusion–positive NSCLC; however, long-term responses are modest and therefore this is a population of high unmet need.

Pralsetinib a selective RET inhibitor has demonstrated robust efficacy with a manageable side effect profile in the Phase I/II, single-arm ARROW study in both treatment-naive patients and platinum-exposed patients with RET fusion–positive NSCLC. AcceleRET aims to investigate the safety and efficacy of pralsetinib in the first-line metastatic setting in the context of a randomized Phase III trial.

This Phase III study is designed as a randomized, open-label, efficacy, and safety study. Participants who meet all study eligibility criteria will be randomly assigned in a 1:1 ratio to receive either pralsetinib or a platinum-containing regimen from an investigators' choice list of SOC platinum-containing anticancer treatment regimens, with or without pembrolizumab (see Section 4.1.1). Random assignment of participants minimizes bias and helps ensure that both known and unknown risk factors are distributed evenly between treatment arms.

The study is not blinded because the distinct methods for study drug administration (capsules for pralsetinib compared with IV infusion of investigator's choice of SOC platinum-containing anticancer treatment regimens) and the variable dosing durations make effective blinding challenging.

An assessment of whether pralsetinib improves PFS relative to an investigator's choice of SOC platinum-containing anticancer treatment regimens is the primary objective of the study. Response assessments will be based on standard response criteria (RECIST v1.1; see Appendix 8).

Key secondary endpoints include OS and ORR. Additional secondary endpoints include duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR), and safety and tolerability of pralsetinib.

4.2.2 Justification for Dose

In the dose-finding Phase I portion of the ARROW study, 52 patients received pralsetinib at doses ranging from 30 to 600 mg QD, with the maximum tolerated dose (MTD) determined to be 400 mg QD. Of the 4 patients treated with 600 mg pralsetinib QD, 2 patients experienced dose-limiting toxicities (DLTs), Grade 3 hyponatremia and Grade 3 hypertension. Although both DLTs were reversible, per the protocol guidelines, 600 mg QD exceeded the MTD, and the MTD of pralsetinib was determined to be 400 mg QD. The overall safety across doses ranging from 60 to 400 mg QD was favorable. Most adverse events were Grade 1; the most commonly reported adverse events in Phase I portion of the study were constipation (reported in 24% of patients), increased ALT (22%), increased (AST 20%), and hypertension (16%). Pralsetinib demonstrated rapid absorption, a long drug-elimination half-life, and a dose-dependent increase in exposure and pathway inhibition. Exposure at the 400-mg MTD provided sustained coverage above the predicted tumor and brain RET IC90. Based on these results, 400 mg QD will be the dose of pralsetinib patients will receive in this study.

Participants will be treated with carboplatin, cisplatin, pemetrexed, gemcitabine, paclitaxel or nab-paclitaxel, and pembrolizumab according to approved dosage recommendations and SOC.

4.2.3 Rationale for Control Group

The immunophenotype of RET-rearranged lung cancers is characterized by low levels of PD-L1 expression and low tumor mutational burden in the majority of patients. Overall outcomes with single- and dual-agent immunotherapy are poor, and therefore these options were excluded as control group treatment regimens within the context of this study. In a retrospective case study from Memorial Sloan Kettering Cancer Center, no responses to immune checkpoint inhibitors were observed in patients with metastatic RET-rearranged lung cancers and the best objective response to therapy in most patients was progressive disease (Offin et al. 2019). Poor outcomes with immune checkpoint inhibitors were also noted in the international IMMUNOTARGET registry in the context of metastatic RET-rearranged NSCLC. The ORR observed in patients with RET alterations was 6%, with a median PFS of 2.1 months (Mazieries et al. 2019).

These findings are consistent with a growing body of evidence uncovering poor outcomes with immune checkpoint inhibition in selected oncogene-addicted lung cancers. In EGFR-mutant and ALK-rearranged lung cancers, early data on the decreased activity (compared with unselected cancers) of immunotherapy resulted in the exclusion of patients with such tumors in registration-enabling studies.

According to treatment guidelines, patients who have RET rearrangement–positive NSCLC should be treated with a RET inhibitor where available (NCCN 2020). The lack of globally approved therapy targeting RET, coupled with low rates of testing for RET, leads to most patients with RET rearrangement being treated as no actionable

oncogenic mutation, that is, with platinum-based chemotherapy, with or without pembrolizumab.

For patients with adenocarcinoma, pemetrexed is the preferred platinum partner shown in a Phase III non-inferiority randomized study comparing OS following treatment with pemetrexed with cisplatin compared with gemcitabine with cisplatin. In the study, the treatment by histology analysis showed that in non-squamous NSCLC, OS was significantly improved in the cisplatin/pemetrexed arm compared with the cisplatin/gemcitabine arm ($n=847$; 12.6 vs. 10.9 months, respectively; hazard ratio [HR]: 0.84; 95% CI: 0.71 to 0.99; $p=0.03$) (Scagliotti et al. 2008).

In a retrospective series, patients with advanced RET-rearranged lung cancers, systemic therapy with pemetrexed-based chemotherapy was shown to be active. The ORR of 45% and a median PFS of 19 months were observed relative to a historical response rate of 30% with platinum-doublet chemotherapy (Drillon et al. 2016).

The benefit of platinum-based chemotherapy with pemetrexed and/or pembrolizumab has been demonstrated in KEYNOTE-189, a Phase III study of 616 patients with metastatic non-squamous NSCLC, regardless of PD-L1 status without prior systemic therapy. Patients were randomized to receive platinum chemotherapy and pemetrexed plus pembrolizumab or placebo every 3 weeks for four cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy. The OS at 12 months was 49.4% (95% CI: 42.1% to 56.2%) in the placebo-platinum therapy and pemetrexed arm (HR for death: 0.49; 95% CI: 0.38 to 0.64; $p<90.001$), and 69.2% (95% CI: 64.1 to 73.8) in the pembrolizumab and chemotherapy arm (Gandhi et al. 2018).

The benefit of platinum therapy with paclitaxel, nab-paclitaxel, and pembrolizumab was shown in KEYNOTE-407, a Phase III study of 559 patients with untreated metastatic squamous NSCLC. Patients were randomized to receive either pembrolizumab in combination with chemotherapy or chemotherapy and placebo. The combination of pembrolizumab and chemotherapy showed improved clinical benefit over chemotherapy plus placebo: OS (median OS: 17.1 months; 95% CI: 14.4 to 19.9 months vs. 11.6 months; 95% CI: 10.1 to 13.7 months; HR: 0.71; 95% CI: 0.58 to 0.88 months) and PFS (median PFS: 8.0 months; 95% CI: 6.3 to 8.4 months vs. 5.1 months; 95% CI: 4.3 to 6.0; HR: 0.57; 95% CI: 0.47 to 0.69) (Paz-Ares et al. 2020).

Platinum therapy with gemcitabine is an accepted approved regimen for patients with squamous cell carcinoma. Although comparable efficacy has been observed with several platinum-based regimens with third-generation cytotoxic agents (paclitaxel, gemcitabine, docetaxel, vinorelbine), gemcitabine-based platinum combinations have more favorable safety profiles. The benefit of gemcitabine in combination with platinum therapy in metastatic squamous NSCLC has also been shown in a Phase III, non-inferiority, randomized study comparing OS following treatment with pemetrexed

with cisplatin versus gemcitabine with cisplatin. OS for cisplatin/pemetrexed was non-inferior to cisplatin/gemcitabine (median OS: 10.3 vs. 10.3 months, respectively; HR: 0.94; 95% CI: 0.84 to 1.05) in the combined histology population. However, in a treatment by histology analysis, the study found that for patients with squamous NSCLC, the OS gain was slightly higher with cisplatin and gemcitabine compared with cisplatin and pemetrexed (OS: 10.8 vs. 9.4 months, respectively; HR: 1.23; 95% CI: 1.00 to 1.51; $p = 0.05$) (Scagliotti et al. 2008).

Second-line treatment options for patients with non-squamous and/or squamous NSCLC show limited clinical activity. Single-agent checkpoint inhibition in this setting results in an ORR ranging from 14%–20% and a PFS of 2.3–5.2 months (Borghaei et al. 2015; Brahmer et al. 2015; Herbst et al. 2016; Fehrenbacher et al. 2018).

In this study, investigators will have the option to select from a choice of SOC platinum-containing anticancer treatment regimens aligned with local regulations and institutional guidance.

4.2.4 Rationale for Biomarker Assessments

RET fusions are oncogenic drivers in 1%–2% of NSCLCs. The most common RET fusion in NSCLC is KIF5B-RET, but many other RET fusion partners have been reported (Ou et al. 2020). KIF5B-RET fusion can occur in different variants depending on the point of fusion (Kohno et al. 2012). Different RET fusion variants or RET fusion partners as well as genomic alterations in tumor-related genes that exist prior to RET inhibitor treatment may influence the efficacy of pralsetinib treatment. Several molecular mechanisms of resistance to tyrosine kinase inhibitors (TKIs) have been implicated in drug resistance, including target modification (e.g., acquired mutations within the kinase domain), gene amplification or overexpression, or activation of bypass signaling pathways (Chen and Fu 2011; Lovly 2015). RET mutations and mutations in cancer-related genes may appear as a result of biologic selection pressure on tumor cells induced by RET TKI treatment. RET mutation-mediated resistance in single patients has been reported for MKIs (Wirth et al. 2019). Mechanisms of acquired resistance to selective RET TKIs, such as selpercatinib and pralsetinib, remain mainly unknown. However, the emergence of a RET solvent front mutation (G810) together with the re-emergence of the RET gatekeeper mutation (V804M) during selpercatinib treatment has been reported (Solomon et al. 2020).

Understanding different RET-driver mutations influence on treatment efficacy and underlying resistance mechanisms to pralsetinib is critical to develop strategies to optimize treatment benefit and to overcome resistance.

Genomic alterations and copy number variations that may lead to drug resistance can be detected in nucleic acids from tissue and in circulating nucleic acids from plasma. Tumor nucleic acids (e.g., circulating tumor DNA [ctDNA]) are shed into the circulation and can be analyzed by next-generation sequencing (NGS). Circulating tumor nucleic

acids may be used to help to elucidate the molecular profile of RET fusion-positive NSCLC and to detect changes in the molecular profile during RET TKI treatment and at progression.

Comprehensive diagnostic tests are required to test patients with NSCLC for rare targetable oncogenic driver alterations to select the best treatment option for their disease. Comprehensive tissue and blood-based companion diagnostic (CDx) tests for pralsetinib are essential to identify patients with RET fusion-positive NSCLC who can benefit from this targeted treatment. Blood-based assays to detect RET and other oncogenic driver alterations will provide a diagnostic testing option for patients who do not have sufficient or no tumor tissue available for biomarker testing. Additionally, blood-based testing of changes in RET or cancer-related genes from circulating tumor nucleic acids will provide a less-invasive option for participants to be tested for their tumor mutational status during treatment and at tumor progression. Data generated may support registration of tissue and plasma NGS assays as a CDx for pralsetinib in RET fusion–positive NSCLC.

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

4.3 END OF STUDY DEFINITION

The Sponsor has decided to prematurely terminate Study BO42864. The end of this study is defined as the date when the last participant, last visit occurs.

4.4 DURATION OF PARTICIPATION

The Sponsor has decided to prematurely terminate Study BO42864. The duration of participation for each participant will depend on the treatment received:

- Participants receiving pralsetinib can remain on the study until disease progression as assessed by the investigator, until continued access solutions for pralsetinib are available, pralsetinib is no longer available, or for reasons as described in Section 7.2, whichever comes first.
- Participants receiving SOC platinum-containing anticancer treatment should be withdrawn from the study promptly. In the event that the SOC treatment regimen used within the study is not available to the participant after withdrawal, the participant may remain in the study and continue to receive the SOC treatment but must discontinue, at the latest, by the time the last patient receiving pralsetinib has discontinued from the study. Investigators will be given advanced notice of this timepoint. Additional reasons for study discontinuation for participants that are eligible to remain in the study are described in Section 7.2.

5. STUDY POPULATION

Approximately 226 participants are planned to be enrolled and randomized in a 1:1 ratio to one of the following two arms:

- Arm A: approximately 113 participants randomized to receive pralsetinib
- Arm B: approximately 113 participants randomized to receive a platinum-containing chemotherapy regimen from an investigator's choice list of SOC regimens

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

5.1 INCLUSION CRITERIA FOR ALL PARTICIPANTS

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

- Participant provides signed informed consent (as described in Appendix 1) to participate in this study, which includes compliance with the requirements and restrictions listed in the Informed Consent Form and in this protocol.
- Participant must be age ≥ 18 years at the time of signing Informed Consent Form.
- Participant has pathologically or cytologically confirmed, definitively diagnosed, locally advanced unresectable NSCLC (i.e., Stage IIIB not eligible for definitive chemoradiotherapy) or metastatic NSCLC (i.e., Stage IV), per the Union Internationale Contre le Cancer/American Joint Committee on Cancer staging system (Amin et al. 2017) of either squamous or non-squamous histology based on the major histologic component that has not been treated with systemic anticancer therapy for metastatic disease. For further details on testing methods, refer to Section 8.10.
- Participant has documented RET fusion that meets one of the following two criteria:
  - Documented RET fusion using either tissue or plasma, as determined by an appropriate validated local test performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified or equivalent accredited diagnostic laboratory. For details of acceptable testing methods, see Section 8.10.
  - Documented RET fusion by a positive result from tumor tissue testing performed centrally by Foundation Medicine (FMI) clinical trial assay or an alternate, approved central laboratory for that region.
- The participant agrees to provide preferably adequate tumor tissue (archived, if available, or a fresh biopsy) or if tumor tissue cannot be obtained, a fixed and embedded cell pellet from pleural effusion would be acceptable for central confirmation of RET fusion status using an NGS-based assay. If no adequate tumor material is available and a new biopsy is not feasible, the participant will not be eligible for enrollment. This specimen must be accompanied by the full laboratory report of the RET fusion local test and must also be submitted within 2 weeks of enrollment for confirmation of RET status by central testing.

- A representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or a target of 15–20 slides containing unstained, freshly cut, serial sections is required for participation in this study.
  - A minimum of 10–14 slides is acceptable if the slides meet the tissue requirements in Section 8.10. Notify the Medical Monitor if less than 15 slides are available.
  - Note: If only a fixed and embedded cell pellet from pleural effusion is available it is highly recommended to submit the entire FFPE block for processing at the central lab as this sample type is more challenging to process with NGS.
- Participant has an ECOG Performance Status 0 or 1 (see Appendix 7).
- Participants who have a negative HIV test at screening, with the following exception: Individuals with a positive HIV test at screening are eligible, provided they are stable on anti-retroviral therapy, have a CD4 count $\geq$200/μL, and have an undetectable viral load.
- Participant has measurable disease, as determined by the local site investigator or radiologic assessment according to RECIST v1.1 (see Appendix 8).
  - Lesions located in a previously irradiated area are considered measurable if progression has been demonstrated after irradiation.
- Participant cannot have received any prior anticancer therapy for metastatic disease.
  - Participants can have received previous anticancer therapy (except a selective *RET* inhibitor) in the neoadjuvant or adjuvant setting but must have experienced an interval of at least $\geq$6 months from completion of therapy to recurrence.
  - Participants who have received previous immune checkpoint inhibitors in the adjuvant setting or consolidation therapy following chemoradiation are not allowed to receive pembrolizumab if randomized to Arm B.
- Participant is an appropriate candidate for and agrees to receive one of the investigator choice platinum-based anticancer regimens if randomized to Arm B.
- For women of childbearing potential: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:
  - Women must remain abstinent or use a highly effective method of non-hormonal contraception with a failure rate of $<$1% per year during the treatment period and for a period of a minimum of 14 days after the final dose of pralsetinib. The duration of contraceptive methods for participants receiving SOC platinum-containing anticancer treatment regimens is as indicated in the respective applicable labeling documents (refer to Appendix 4, Section A4–1).
  - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (i.e., $\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause, as determined by the investigator

(e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  - Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male partner sterilization, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agree to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year, during the treatment period and for 7 days after the final dose of pralsetinib to avoid exposing the embryo. With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 7 days after the final dose of pralsetinib to avoid exposing the embryo. Men must refrain from donating sperm during this same period. The duration of contraceptive methods for participants receiving investigator's choice of SOC platinum-containing anticancer treatment is as indicated in the respective applicable labeling documents (refer to Appendix 4, Section A4–2).
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

5.2 EXCLUSION CRITERIA FOR ALL PARTICIPANTS

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

- Participant's tumor has any additional known primary driver alterations other than RET, such as targetable mutations of EGFR, ALK, ROS1, MET, and BRAF. Investigators should inform the Medical Monitor about the enrollment of participants with tumors having comutations.
- Participant previously received treatment with a selective *RET* inhibitor.
- Participant received radiotherapy or radiosurgery to any site within 14 days before randomization or more than 30 Gy of radiotherapy to the lung in the 6 months before randomization.

- Participants with a history of pneumonitis of non-infectious etiology within the last 12 months.
- Participants with autoimmune disease that requires systemic therapy (excluding thyroid, vitiligo).
- Participants with autoimmune disease within 2 years of study enrollment are not eligible for the pembrolizumab-containing regimen.
- Participants with a medical condition that requires immunosuppression.
- Participant has either CNS metastases or a primary CNS tumor that is associated with progressive neurological symptoms or requires increasing doses of corticosteroids to control the CNS disease.
  - If a participant requires corticosteroids for management of CNS disease, the dose must be stable for the 2 weeks prior to Day 1 of Cycle 1.
- Participant has significant cardiovascular disease, as evidenced by any of the following conditions:
  - Participant has a QT interval corrected through the use of Fridericia's formula (QTcF) $>$480 ms.
  - Participant has a history of prolonged QT syndrome or torsades de pointes.
  - Participant has a familial history of prolonged QT syndrome.
  - Participant has clinically significant, uncontrolled, cardiovascular disease, including Grade III or IV congestive heart failure according to the New York Heart Association (NYHA) classification; myocardial infarction or unstable angina within the previous 6 months, uncontrolled hypertension, or clinically significant, uncontrolled arrhythmias, including bradyarrhythmias that may cause QT prolongation (e.g., Type II second-degree or third-degree heart block).
- Participant requires treatment with a prohibited medication or herbal remedy (as specified in Section 6.8.3) that cannot be discontinued at least 2 weeks prior to the start of study drug administration.
  - Pralsetinib may be started within 14 days of stopping a prohibited medication if considered by the investigator to be safe and in the best interest of the participant. Inform the medical monitor if you are considering administering pralsetinib within 14 days of stopping a prohibited medication.
- Participant received treatment with hematopoietic growth factor support within 14 days of the first dose of study drug.
- Participant has had a major surgical procedure within 14 days of the first dose of study drug or is planned to have such procedure during the study period.
  - Procedures, such as central venous catheter placement, tumor needle biopsy, and feeding tube placement, are not considered major surgical procedures.
- Participant has had a history of another primary malignancy that has been diagnosed or required therapy within the past 3 years prior to randomization.

- The following prior malignancies are not exclusionary: completely resected basal cell and squamous cell skin cancer, curatively treated localized prostate cancer, curatively treated localized thyroid cancer, and completely resected carcinoma in situ of any site.

- Participant has any of the following within 14 days prior to the first dose of study drug:
  - Platelet count $< 75 \times 10^9$/L
  - ANC $< 1.0 \times 10^9$/L
  - Hemoglobin < 9.0 g/dL

  RBC transfusion and erythropoietin may be used to reach at least 9.0 g/dL but must have been administered at least 2 weeks before the first dose of study drug.
  - AST or ALT $> 3 \times$ the upper limit of normal (ULN) if no hepatic metastases are present; $> 5 \times$ ULN if hepatic metastases are present
  - Total bilirubin $> 1.5 \times$ ULN; $> 3 \times$ ULN in presence of Gilbert disease
  - Estimated (according to the Cockcroft-Gault formula) or measured creatinine clearance < 45 mL/min
  - Total serum phosphorous > 5.5 mg/dL
- Participant has a known hypersensitivity to cisplatin, carboplatin, pemetrexed, or pembrolizumab (for participants with NSCLC of non-squamous histology only), or carboplatin, gemcitabine, pembrolizumab, paclitaxel, or nab-paclitaxel (for participants with NSCLC of squamous histology only).
- Participant with a serious infection requiring systemic antibiotics within 7 days prior to initiation of study treatment, or any active infection that, in the opinion of the investigator, could impact patient's safety.
  - In the setting of a pandemic or epidemic, screening for active infections should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., ASCO or ESMO).
- Participant has an active, uncontrolled infection (viral, bacterial, or fungal).
  - Participants with controlled infections who are stable on treatment may be eligible if the benefit–risk assessment is justified, and permission is granted from the Sponsor.
- Participant has positive hepatitis C virus (HCV) antibody test at screening.
  - Participants positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
- Participant has positive hepatitis B surface antigen (HBsAg) test at screening.
  - Participants with a previous hepatitis B virus (HBV) infection or resolved HBV infection (hepatitis B core antibody [HBcAb] positive, but negative HBsAg) are eligible only if the HBV DNA test is negative.

- Participant is unwilling or unable to comply with scheduled visits, study drug administration plan (including the inability or unwillingness to swallow capsules), laboratory tests, or other study procedures and study restrictions.
- Participant is pregnant, as documented by a serum β-human chorionic gonadotropin (βhCG) pregnancy test consistent with pregnancy obtained within 7 days before the first dose of study drug.
  - Participants with β-hCG values that are within the range for pregnancy but are not pregnant (false–positives) may be enrolled with written consent of the Sponsor after pregnancy has been ruled out. Women of non-childbearing potential (postmenopausal for more than 1 year, documented bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) do not require a serum β-hCG test.
- Participant is breastfeeding.
- Participant with concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study, or during the follow-up period of an interventional study
- Participant has had a prior or has an ongoing clinically significant illness, medical condition, surgical history, physical finding, or laboratory abnormality that, in the investigator's opinion, could affect the safety of the participant, alter the absorption, distribution, metabolism, or excretion of the study drug, or impair the assessment of study results.

5.3 CROSSOVER ELIGIBILITY CRITERIA

Following the sponsor's decision to prematurely terminate the study, the option for participants in Arm B (SOC) to crossover to Arm A (pralsetinib) has been removed as of protocol version 5.

5.4 LIFESTYLE CONSIDERATIONS

5.4.1 Meals and Dietary Restrictions

This study has the following meal and dietary restrictions:

Participants in Arm A treated with pralsetinib should refrain from consumption of grapefruit or grapefruit juice, during treatment.

5.4.2 Caffeine, Alcohol, and Tobacco

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

5.4.3 Activity

This study has no activity restrictions.

5.4.4 Contraception Requirements

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

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. A minimum set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from health authorities. Minimum information includes demographics, screen failure details, eligibility criteria, and any pretreatment serious adverse event.

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per individual) at the investigator's discretion. Rescreened participants will be assigned the same patient number as for the initial screening.

Individuals are not required to re-sign the consent form if they are re-screened within 30 days after previously signing the consent form. The investigator will record reasons for screen failure in the screening log (see Section 8).

6. STUDY TREATMENTS AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

In this study, pralsetinib, and the comparators carboplatin, cisplatin, gemcitabine, pemetrexed, paclitaxel, nab-paclitaxel, and pembrolizumab are considered investigational medicinal products (IMPs). Appendix 13 identifies all IMPs for this study.

6.1 STUDY TREATMENTS ADMINISTERED

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

Table 5 Study Treatment Description

	Pralsetinib	Carboplatin [a]	Cisplatin [a]	Pemetrexed [a]	Pembrolizumab [a]	Gemcitabine [a]	Paclitaxel [a]	Nab-Paclitaxel [a]
Use	Experimental	Comparator	Comparator	Comparator	Comparator	Comparator	Comparator	Comparator
Type of medicinal product	IMP	IMP	IMP	IMP	IMP	IMP	IMP	IMP
Formulation	Capsule	Concentrate for solution for infusion	Concentrate for solution for infusion	Powder for concentrate for solution for infusion	Concentrate for solution for infusion	Powder for solution for infusion	Concentrate for solution for infusion	Powder for suspension for infusion
Unit dose strength	100 mg	450 mg	50 mg	500 mg	100 mg	1000 mg	150 mg	100 mg
Dosage level(s)	400 mg QD	Target AUC of 5 mg • min/mL Q3W [b]	75 mg/m^2 Q3W	500 mg/m^2 Q3W	200 mg Q3W	1250 mg/m^2 Days 1 and 8 of each cycle	200 mg/m^2 Q3W [c]	100 mg/m^2 on Day 1, 8, and 15 of each cycle
Labeling	Per local requirements							
Route of administration	Oral	IV injection or infusion	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion	IV infusion
Packaging	HDPE bottles containing a desiccant and a child-resistant closure	Vials: Each vial will be labeled as required per country requirement.	Vials: Each vial will be labeled as required per country requirement.	Vials: Each vial will be labeled as required per country requirement.	Vials: Each vial will be labeled as required per country requirement.	Vials: Each vial will be labeled as required per country requirement.	Vials: Each vial will be labeled as required per country requirement.	Vials: Each vial will be labeled as required per country requirement.
Source	Sponsor	Sponsor or locally by the trial site, subsidiary, or designee						
Storage conditions	Refer to the pharmacy manual.							

Table 5 Study Treatment Description (cont.)

AUC = area under the concentration–time curve; HDPE = high-density polyethylene; IMP = investigational medicinal product; Q3W = every 3 weeks; QD = once a day; SOC = standard of care.

[a] Dosing information and handling procedures for the investigator's choice SOC anticancer treatment regimens should follow the guidance provided in the product label and institutional SOC (see Appendix 1).

[b] For participants with squamous NSCLC using the pembrolizumab + carboplatin + paclitaxel or nab-paclitaxel regimen, the dose of carboplatin is target AUC of 6 mg • min/mL (see Section 6.1.2.1).

[c] For participants of Asian race/ethnicity: 175 mg/m^2 administered by IV infusion.

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 5.

6.1.1 Participants in Arm A and Participants Who Crossover from Arm B to Receive Pralsetinib

Participants randomized to the pralsetinib (Arm A) or participants originally randomized to Arm B who cross over will receive 400 mg pralsetinib PO QD. Dosing will be continuous, with no inter-cycle rest periods.

Doses of pralsetinib may be modified or discontinued for toxicity as described in Section 6.5 and Appendix 1, Section A5–1.1.1.

Pralsetinib doses should be administered with a glass of water in a fasted state, with no food intake from 2 hours before until 1 hour after study drug administration. Participants should be instructed to swallow study drug whole and to not chew the study drug.

Each dose should be administered in the morning, at approximately the same time each day. If a planned dose of pralsetinib is missed, participants can make up that dose unless the next dose is due within 12 hours. Resume the regular daily dose schedule for pralsetinib the next day. If a participant vomits during or after taking pralsetinib, re-dosing is not permitted until the next scheduled dose.

Participants will be dispensed the appropriate number of packaged and labeled pralsetinib bottles on Day 1 to allow dosing for 21-day treatment cycles; alternatively, participants may be dispensed the appropriate bottle(s) until the next scheduled visit. Participants must return all unused capsules (or the empty bottles) at each scheduled visit.

All participants should complete the drug (pralsetinib) self-administration diary and bring it to each site visit.

6.1.2 Investigator's Choice of SOC Platinum-Containing Anticancer Treatment Regimens: For Participants in Arm B

6.1.2.1 Administration

Participants randomized to the chemotherapy arm (Arm B) will receive one of six SOC platinum-containing anticancer treatment regimens at the study center as chosen by the treating investigator on the basis of NSCLC histology.

For participants with NSCLC of non-squamous histology:

- Carboplatin in combination with pemetrexed (with vitamin supplementation): Participants should receive pemetrexed 500 mg/m^2 followed by carboplatin to target area under the concentration–time curve (AUC) of 5 mg • min/mL both on Day 1 every 3 weeks (Q3W) for 4 or 6 cycles with an option to continue maintenance pemetrexed 500 mg/m^2 Q3W until progression or up to a maximum of 2 years.

- Cisplatin in combination with pemetrexed (with vitamin supplementation): Participants should receive pemetrexed 500 mg/m^2 followed by cisplatin 75 mg/m^2 both on Day 1 Q3W for 4 or 6 cycles with an option to continue maintenance pemetrexed 500 mg/m^2 Q3W until progression or for up to a maximum of 2 years.
- Pembrolizumab in combination with carboplatin and pemetrexed (with vitamin supplementation): Participants should receive pembrolizumab 200 mg together with pemetrexed 500 mg/m^2 (with vitamin supplementation) and carboplatin AUC of 5 mg • min/mL all on Day 1 Q3W for 4 or 6cycles followed by pembrolizumab 200 mg together with pemetrexed 500 mg/m^2 Q3W until progression or for up to a maximum of 2 years.
- Pembrolizumab in combination with cisplatin and pemetrexed (with vitamin supplementation): Participants should receive pembrolizumab 200 mg together with pemetrexed 500 mg/m^2 (with vitamin supplementation) and cisplatin 75 mg/m^2 all on Day 1 Q3W for 4 or 6 cycles followed by pembrolizumab 200 mg together with pemetrexed 500 mg/m^2 Q3W until progression or for up to a maximum of 2 years.

For participants with NSCLC of squamous histology, participants will receive one of following three SOC platinum-containing anticancer treatment regimens at the study center as chosen by the treating investigator:

- Carboplatin in combination with gemcitabine: Participants should receive carboplatin to target AUC of 5 mg • min/mL on Day 1 of each 3-week cycle and gemcitabine 1250 mg/m^2 on Days 1 and 8 of each 3-week cycle for 4 or 6 cycles.
- Cisplatin in combination with gemcitabine: Participants should receive cisplatin 75 mg/m^2 on Day 1 of every 3-week cycle and gemcitabine 1250 mg/m^2 on Days 1 and 8 of each 3-week cycle for 4 or 6 cycles.
- Carboplatin in combination with paclitaxel/nab-paclitaxel and pembrolizumab: Participants should receive pembrolizumab 200 mg together with carboplatin to target AUC of 6 mg • min/mL and paclitaxel 200 mg/m^2 on Day 1, or nabpaclitaxel 100 mg/m^2 on Days 1, 8, and 15 of each 3-week cycle for 4 or 6 cycles, followed by pembrolizumab 200 mg Q3W until progression or for up to a maximum of 2 years.

Each study site will administer chemotherapy for 4 or 6 cycles based on local guidelines. The selected chemotherapy agent should remain the same for all cycles (e.g., participants who start treatment with cisplatin should remain on cisplatin and not switch to carboplatin or vice versa and participants that start treatment with nab-paclitaxel should not switch to paclitaxel). However, for participants who experience unacceptable toxicity with the selected platinum chemotherapy, a switch may be considered. If a chemotherapy switch is considered, notify the Medical Monitor.

Doses of investigator's choice of SOC platinum-containing anticancer therapy regimens may be modified or discontinued due to toxicity as described in the product labels and on institutional standards.

Participants should receive appropriate hydration, premedication, and supportive care measures as deemed necessary by the treating Investigator and consistent with the SOC for their institution.

Administration of SOC anticancer therapy will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 6.

6.1.3 Timing of Dose Administration

Study treatment should be administered on Day 1 of each cycle after all procedures and assessments have been completed. Study treatment can be administered within ±4 days of the targeted Day 1 for each cycle, except Cycle 2 (when study treatment can be administered ± 1 day of the targeted Day 1). For Cycle 1, study treatment should be started within 7 days of randomization (see the schedule of activities in Table 1).

Cisplatin

Cisplatin 75 mg/m^2 should be infused approximately 30 minutes after the pemetrexed infusion Q3W for the first 4 or 6 cycles and should be immediately preceded and followed by hydration procedures and administered according to local prescribing information and institutional standards.

Carboplatin

Carboplatin AUC 5 mg • min/mL (or 6 mg.ml/min for participants with squamous NSCLC using the Carboplatin in combination with paclitaxel/nab-paclitaxel and pembrolizumab regimen) will be administered as an IV infusion over 15–60 minutes Q3W for 4 or 6 cycles immediately after pemetrexed as per local prescribing information and institutional standards.

Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes Q3W as per prescribing information and institutional standards for up to 2 years unless stopped earlier due to centrally confirmed disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation for other reasons.

All participants taking pemetrexed should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below:

- Folic acid 350–1000 μg PO: At least five doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the final dose of pemetrexed.
- Vitamin B12 1000 μg intramuscular (IM) injection: in the week preceding the first dose of pemetrexed and once every three cycles thereafter.
  - Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.

- Dexamethasone prophylaxis 4 mg (or equivalent) PO twice per day: the day before, day of, and day after pemetrexed administration.
  - Higher or additional doses are permitted for anti-emetic prophylaxis during Cycles 1–4.

Pemetrexed supplementation may be adjusted as deemed necessary by the treating Investigator and consistent with the local prescribing information and/or the institutional standards.

Pembrolizumab

Pembrolizumab should be administered as a 200 mg IV infusion over 30 minutes Q3W as per local prescribing information and institutional standards, for up to 2 years unless stopped earlier owing to centrally confirmed disease progression, unacceptable toxicity, withdrawal of consent, or discontinuation for other reasons.

When administering pembrolizumab in combination with chemotherapy, administer pembrolizumab before chemotherapy when given on the same day.

Paclitaxel

In general, paclitaxel will be administered intravenously at a dose of 200 mg/m^2 over 3 hours Q3W as per local prescribing information and institutional standards, for up to 4 or 6 cycles, followed by carboplatin. Participants of Asian race/ethnicity will receive a lower starting dose of paclitaxel at 175 mg/m^2 by IV infusion over 3 hours. The term "Asian race/ethnicity" refers to a pan-ethnic/racial group that includes diverse populations who either live or have ancestral origins in East Asia, Southeast Asia, or South Asia. The applicability of such term in a particular participant will be at the discretion of the treating investigator and should be based on the participant's clinical characteristics and country of origin.

When administering paclitaxel in combination with pembrolizumab and chemotherapy, administer pembrolizumab before paclitaxel followed by carboplatin.

Sites should follow their institutional standard of care for dose adjustments in the event of participant weight changes. For paclitaxel infusion, exceptions to the infusion time of 3 hours will be allowed for sites that have an institutional policy of infusing paclitaxel more quickly (over 90 minutes) or more slowly (up to 4 hours for the first infusion).

All participants taking paclitaxel should receive the appropriate corticosteroid prophylaxis as listed below:

- Dexamethasone 20 mg (or equivalent) PO approximately 12 and 6 hours before paclitaxel administration
  - Participants may be treated with dexamethasone 10–20 mg IV within 1 hour prior to paclitaxel infusion if the participant did not take the oral dexamethasone

- Diphenhydramine 50 mg (or equivalent) administered by IV infusion 30–60 minutes prior to paclitaxel administration
- Cimetidine 300 mg or ranitidine 50 mg (or equivalent) administered by IV infusion 30–60 minutes prior to paclitaxel administration

Paclitaxel supplementation may be adjusted to as deemed necessary by the treating Investigator and consistent with the local prescribing information and/or the institutional standards.

Nab-Paclitaxel

Nab-paclitaxel will be administered intravenously at a dose of 100 mg/m^2 over 30 minutes on Days 1, 8, and 15 of each 21-day cycle, as per local prescribing information and institutional standards for up to 4 or 6 cycles. Nab-paclitaxel should be completely administered before initiating carboplatin dose.

Sites should follow their institutional standard of care for determining the nab-paclitaxel dose for participants who are obese and for dose adjustments in the event of participant weight changes. The infusion site should be closely monitored for possible infiltration during drug administration.

Gemcitabine

Gemcitabine 1250 mg/m^2 will be administered intravenously over 30 minutes on Days 1 and 8 of each 21-day cycle for the first 4 or 6 cycles according to the prescribing information and institutional standards.

Guidelines for medical management of infusion-related reactions and injection-site reactions are provided in Appendix 3, Section A3–6.7.

Additional Medication for Participants in Arm B Who Receive Pemetrexed and Nab-Paclitaxel

Participants in Arm B who receive pemetrexed and nab-paclitaxel should receive the appropriate supplementation as described in Section 6.1.3 or per institutional guidance.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

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

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using an interactive web-based response system (IwRS) by returning the appropriate

documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs.
All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

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

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

Refer to the pharmacy manual and/or the Pralsetinib Investigator's Brochure or local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

This study is open-label; potential bias will be reduced by the central randomization.

Participants who meet all study eligibility criteria will be randomly assigned in a 1:1 ratio to receive pralsetinib PO QD or an SOC platinum-containing anticancer treatment regimen from an investigator’s choice from a list of SOC regimens.

The randomization assignment will be implemented by an IwRS. Before the study is initiated, the log in information and directions for the IwRS will be provided to each site.

Randomization will be stratified by the following:

- History of brain metastasis (yes vs. no)
- ECOG Performance Status (0 vs. 1)
- Intended use of pembrolizumab if randomized to the control arm (yes vs. no)

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the electronic Case Report Form (eCRF). The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

When participants self-administer pralsetinib at home, compliance with study treatment will be assessed. Participant compliance with study drug administration will be assessed at each visit. Compliance with pralsetinib dosing will be assessed by review of dosing diary and counting returned capsules. Deviation(s) from the prescribed dosage regimen should be recorded on the eCRF.

Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Appendix 3.

Participants randomized to the investigator's choice of SOC platinum-containing anticancer regimen arm will receive IV treatment at the study center.

6.5 DOSE MODIFICATION

The dose of pralsetinib can be reduced up to three times for management of drug-related toxicities, as described in Appendix 5, Section A5–1.1.1.

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

The Sponsor will offer continued access to Roche IMP (pralsetinib) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMP (pralsetinib) after completing the study if all of the following conditions are met:

- The participant received Roche IMP during study conduct.
- The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

Eligible participants may be provided access to Roche IMP after completing the study until Roche IMP is no longer available.

A participant will not be eligible to receive Roche IMP (pralsetinib) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for NSCLC with RET fusion–positive tumors.
- The Sponsor has reasonable safety concerns regarding the IMP as a treatment for NSCLC with RET fusion–positive tumors.
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.
- The Roche IMP is no longer manufactured.

In these situations, the investigator and primary care physician will transition the study participant to an alternative therapy in accordance with institutional or local guidelines.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

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

6.7 TREATMENT OF OVERDOSE

Participants should be informed to contact their doctor immediately if they have taken more than the prescribed dose of medication and should hold off taking additional investigational drug until instructed to do so by their study investigator. Clinic staff should be notified immediately, and supportive care should be given if needed and as indicated.

For this study, overdose is defined as the administration of either IMP in a quantity that is higher than the prescribed dose. There is no known antidote for treating an overdose of pralsetinib or any of the comparator drugs. Overdoses will not be considered serious adverse events unless the outcome of the overdose meets the seriousness criteria as defined in Appendix 3. Overdoses should be reported as special situation (see Appendix 3, Section A3–6.11). In the event of an overdose that causes a serious adverse event, the Sponsor should be notified within 24 hours of the investigator's knowledge of the event. The participant should be carefully monitored for potential adverse reactions and symptomatic treatment instituted as per institutional SOC. The investigator will determine if and when dosing should resume.

Decisions regarding dose interruptions or modifications will be made by the investigator on the basis of clinical evaluation of the participant. The Medical Monitor is available to provide advice on trial-related medical questions regarding dose interruption and modifications.

6.8 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment. Concomitant medications will be recorded on the Prior and Concomitant Medication and Therapy eCRF from the time of signing informed consent to 30 days after the final dose.

6.8.1 Permitted Therapies

Medications and treatments, including palliative and supportive care for disease-related symptoms, are permitted during the study.

Participants should be closely monitored, and treatment is to be instituted for disease-related symptoms, as appropriate. Supportive care measures for treating adverse events should be instituted as soon as they are recognized.

In general, investigators may manage a participant's care (including preexisting conditions) through use of supportive therapies, as clinically indicated and per local standard practice, with the exception of prohibited therapies defined in Section 6.8.3 and taking into account cautionary therapies defined in Section 6.8.2. Participants who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen, β_2-adrenergic agonists).

Premedication with antihistamines, antipyretic medications, and/or analgesics may be administered at the discretion of the investigator.

For Participants Treated with Pemetrexed

All participants taking pemetrexed should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below or per institutional standards:

- Folic acid 350–1000 μg PO: at least five doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the final dose of pemetrexed
- Vitamin B12 1000 μg intramuscular injection: in the week preceding the first dose of pemetrexed and once every three cycles thereafter
  - Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.

- Dexamethasone prophylaxis 4 mg (or equivalent) PO twice per day: the day before, day of, and day after pemetrexed administration
  - Higher or additional doses are permitted for anti-emetic prophylaxis during Cycles 1–4.

For Participants Treated with Paclitaxel

All participants taking paclitaxel should receive the appropriate corticosteroid prophylaxis as listed below or per institutional standards:

- Dexamethasone prophylaxis 20 mg (or equivalent) PO approximately 12 and 6 hours before paclitaxel administration
  - Participants may be treated with dexamethasone 10–20 mg IV within 1 hour prior to paclitaxel infusion if the participant did not take the oral dexamethasone
- Diphenhydramine 50 mg (or equivalent) administered by IV infusion 30–60 minutes prior to paclitaxel administration
- Cimetidine 300 mg or ranitidine 50 mg (or equivalent) administered by IV infusion 30–60 minutes prior to paclitaxel administration

For Participants Treated with Nab-Paclitaxel

Anti-emetic medications, anti-allergic measures, and other treatments for concomitant nab-paclitaxel toxicities may be used at the discretion of the investigator, taking into account precautions in the Summary of Product Characteristics.

Refer to the Summary of Product Characteristics (Package Insert) for nab-paclitaxel for all boxed warnings and contraindications.

For Participants Treated with Carboplatin and Cisplatin

Carboplatin and cisplatin are considered to be highly emetogenic. Anti-emetic treatments for nausea and vomiting associated with carboplatin and cisplatin are to be administered in accordance with each product's prescribing information and institutional standards. Anti-emetic treatments for all other chemotherapy regimens may be used at the investigator's discretion and in accordance with local guidelines or equivalent after documented nausea or vomiting has occurred without medications having been used. The choice of anti-emetic treatment, if required, will be made at the investigator's discretion. Antidiarrheal medications may also be used after documented diarrhea has occurred, at the investigator's discretion.

6.8.2 Cautionary Therapy

The following medications are to be used with caution only for participants treated with pralsetinib during the study:

- In vitro metabolism studies in human liver microsomes have demonstrated that pralsetinib is a direct moderate inhibitor and inducer of multiple P450 enzymes (CYP2C8, CYP3A4, and CYP2C9). Pralsetinib is also a time-dependent inhibitor of CYP3A4/5.

- Pralsetinib is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K at clinically relevant concentrations. In participants pralsetinib may alter or increase the plasma concentration of co-administered sensitive CYP2C8, CYP3A4, CYP2C9, Pgp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K substrates.
  - Hence, medications that are sensitive CYP2C8, CYP3A4, CYP2C9, P-gp, BCRP, OATP1B1, OATP1B3, OAT1, MATE1, and MATE2-K substrates with known DDI potential should be used with caution.

Drugs and foods to be used with caution for participants treated with pralsetinib are provided in Appendix 10. The above list of medications is not necessarily comprehensive. The investigator should consult the local prescribing information when determining whether a concomitant medication can be safely administered with study treatment. For cautionary medications related to carboplatin, cisplatin, gemcitabine, pemetrexed, paclitaxel, nab-paclitaxel, and pembrolizumab, refer to the local prescribing information or Summary of Product Characteristics.

In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

6.8.3 Prohibited Therapy and Procedures

The following medications and procedures are prohibited during study treatment:

- For participants treated with pralsetinib: In vitro metabolism studies indicate that pralsetinib oxidation is primarily mediated by CYP3A4 and to a minor extent by CYP1A2 and CYP2D6 and glucuronidation by UGT1A4. As a precaution, strong inhibitors as well as inducers of CYP3A4 are prohibited. Drug transporter studies in cells overexpressing Pgp indicate that pralsetinib is likely also a Pgp substrate. Medications that are strong dual inhibitors of Pgp and CYP3A4 are prohibited.

  Refer to Appendix 10 for a list of prohibited medications and foods.
- Any investigational agent or device other than pralsetinib, including commercially available agents that are investigational for the treatment of the participant's underlying malignancy
- Any antineoplastic treatment other than study drugs
- Any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to randomization and during treatment (for participants receiving pembrolizumab)
- If radiation or surgical excision of a target lesion is determined to be in the best clinical interest of the participant and cannot be avoided, the Medical Monitor should be informed, as radiation or surgical excision of target lesions may render participants unevaluable for further response assessments.

For prohibited medications related to carboplatin, cisplatin, gemcitabine, pemetrexed, paclitaxel, nab-paclitaxel, and pembrolizumab, refer to the local prescribing information and Summary of Product Characteristics (Package Insert).

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional safety assessments. Refer to the schedules of activities (see Section 1.3, Table 1 and Table 2) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Use of an anticancer therapy not required per protocol
- Confirmed progression per the investigator according to RECIST v1.1
- Any event that meets stopping criteria
- Other reasons, including major protocol violation or non-compliance

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

Participants will return to the clinic for an EOT discontinuation visit within 14 days after the final dose of study drug, and for a safety follow-up assessment approximately 30 days after the final dose of study drug or initiates an antineoplastic therapy.

If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study treatment is required by the investigator when a study participant meets abnormal liver tests as outlined in Appendix 3, Section A3–6.6, or if the investigator believes that it is in best interest of the participant when abnormal liver function results not meeting protocol-specified stopping rules.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

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

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

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3, Table 1 and Table 2). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data if not otherwise restricted by local law.

If a participant withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

The Sponsor informed all investigators of the decision of premature study termination on 23 January 2024.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to

return to the clinic, and determine if there are ways to support participant participation.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as presented in Appendix 1, Section A1–9.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site. Any participant who consents to RET testing outside of current SOC should sign the Prescreening Informed Consent Form prior to acquisition of tumor sample. Prescreening may occur any time prior to screening. Participants should wait until the RET results are known before signing the main study Informed Consent Form.

The schedules of activities are provided in Section 1.3, Table 1 for the main treatment period and Table 2 for the crossover treatment period. All clinical and laboratory safety assessments will be assessed by the investigator for clinical significance, and clinically significant findings will be reported as adverse events. Additional safety assessments may be performed when clinically indicated at the investigator's discretion.
Unless otherwise indicated, all assessments must be performed predose at each visit. Whenever a result is questionable, it should be repeated immediately.

- Study procedures and their timing are summarized in the schedules of activities (see Section 1.3, Table 1 and Table 2).
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.
- Adherence to the study protocol requirements, including those specified in the schedule of activities, is essential and required for study conduct. Protocol waivers or exemptions are not allowed.
- All screening evaluations must be completed and reviewed 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 tests, radiologic tumor assessments, bone marrow aspirates and biopsies) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the screening window defined in the schedule of activities.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for presence of toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable. Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

At applicable sites, following Day 1 of Cycle 2 or Day 1 of crossover Cycle 2 certain study assessments may be performed by a MN (mobile nursing) professional at the participant's home or another suitable location to improve access and convenience for participants participating in the study. The Sponsor will select a health-care company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedules of activities (see Section 1.3, Table 1 and Table 2) specify the assessments that may be performed by an MN professional.

8.1 ELIGIBILITY REVIEW AND REGISTRATION

Participants who are candidates for enrollment into the study will be evaluated for eligibility by the investigator to ensure that the inclusion and exclusion criteria (see Sections 5.1 and 5.2, respectively) have been satisfied. The timeframe for obtaining informed consent is provided in the schedule of activities. The investigator will confirm eligibility for all participants before receipt of the first dose of study treatment.

For study eligibility, RET fusion status may be determined locally. However, baseline tumor tissue samples for all participants must also be submitted within 2 weeks of enrollment for confirmation of RET status by central testing.

Pretreatment tumor tissue will be analyzed centrally for analysis of RET fusion status retrospectively and for biomarkers that may correlate with anti-neoplastic activity and resistance. This tissue may be from an archived sample or from a fresh biopsy.

If no local test is available to determine RET eligibility, if approved by the Sponsor, the participant may submit adequate tumor tissue for central testing by a FMI clinical trial assay or an alternate, approved central laboratory for that region.

If a participant is enrolled using local RET testing methods, the following are required:

- Adequate tumor tissue, accompanied by the full laboratory report of the RET fusion local test, must be submitted within 2 weeks of enrollment for central confirmation of RET fusion status. If RET fusion status for enrollment is determined on the basis of tissue determined through the use of F1CDx test or the alternative, approved central laboratory for that region, tissue sample will still be required for other biomarker analysis, but a repeated central F1CDx test (or the alternative, approved central laboratory for that region) will not be required.
- If archived tumor tissue is not available, participants are required to undergo a pretreatment biopsy. If performed after the baseline radiographic imaging, pretreatment biopsies must be taken from a non-target lesion.
- Details regarding where the local assay was performed, the method used, the tissue and specimen type tested, RET fusion details, and local assay name, are to be entered on the corresponding eCRF.

Additional exploratory biomarker research may be performed using residual tumor tissue samples and material derived from these samples in view of developing new genetic and mechanistic biomarkers with documented participant consent.

8.2 DEMOGRAPHIC INFORMATION

The following demographic information will be collected at screening (if allowed per local regulations): year of birth, sex, ethnicity, and race.

8.3 MEDICAL HISTORY

A participant's medical history should be reviewed during screening. This includes, but is not limited to, documentation of diagnosis, including history of disease and other malignancies, responses to prior anti-neoplastic treatments (if available), prior and concomitant medications, and prior and concurrent medical conditions and surgeries. Relevant historical and ongoing medical events should be recorded on the appropriate eCRF. Confirmation that a female participant is of non-childbearing potential is considered relevant medical history.

8.4 EFFICACY ASSESSMENTS

8.4.1 Tumor and Response Evaluations

As of protocol version 5, the tumor assessment schedule will be conducted as per local institutional standard of care and recorded in the eCRF until radiographic disease progression per RECIST v1.1 as assessed by the investigator or discontinuation from the study.

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

8.4.1.1 Radiographic Assessments

Due to the Sponsor's decision to prematurely terminate the study and as of protocol version 5, tumor scans will no longer be collected prospectively by the Sponsor or submitted to a BICR facility as BICR will not be utilized.

Screening assessments must include computed tomography (CT) scans with contrast (per institutional standard operating procedures) of the chest, abdomen, and pelvis. If a CT scan with contrast is contraindicated (e.g., in participants with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with contrast, if feasible) of the abdomen and pelvis should be performed. CT or MRI scans of other disease sites should be performed as clinically indicated.

All participants must undergo an MRI (preferred) or CT scan (with contrast) of the brain at screening and all subsequent tumor visits regardless of the presence or absence of metastases at baseline. In the event of an equivocal CT scan at screening, an MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases. Brain scans should be performed for all participants until disease progression per the schedule of activities.

Participants with known or suspected bone metastases should undergo bone scans or other institutional standard bone imaging at screening and at subsequent tumor assessments as clinically indicated.

At the investigator's discretion, other methods of assessment of disease as per RECIST v1.1 may be used. If a CT scan for tumor assessment is performed in a PET/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Details regarding imaging procedures will be provided in an imaging manual.

Radiographic images collected prior to protocol version 5 will be submitted to a BICR facility for a quality and completeness check, for central review, and for temporary storage prior to transferring images to the Sponsor.

Assessment of response and progression status will be evaluated at each scheduled disease response assessment locally by the investigator using RECIST v1.1 (see Appendix 8), as outlined in the schedule of activities (see Section 1.3, Table 1 and Table 2). Assessments should be performed by the same individual, if possible, to ensure internal consistency across visits. CT or MRI of chest, abdomen, pelvis, and any

other known sites of metastatic disease may be used; however, the same method of assessment used at screening should be utilized throughout the study for each location. CT with IV contrast is the preferred imaging modality, unless a site of disease is better evaluated by MRI. If a participant is not tolerant of IV contrast, non-contrast scans may be performed.

Endpoints (e.g., ORR, PFS, CBR), will be calculated programmatically by the Sponsor on the basis of investigator assessments of response at each specified timepoint.

8.4.2 Eastern Cooperative Oncology Group Performance Status

Determination of ECOG Performance Status will be performed at the visits outlined in the schedule of activities in Section 1.3, Table 1 and Table 2. Refer to Appendix 7 for the ECOG Performance Status Scale.

8.5 SAFETY ASSESSMENTS

8.5.1 Physical Examinations

A complete physical examination will be performed at the screening visit. A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height will also be measured and recorded at least once during screening and does not need to be repeated with each physical examination. Weight should be recorded at each physical examination.

Subsequent physical examinations will be performed as outlined in the schedule of activities and will be disease and adverse event focused. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.5.2 Vital Signs

Vital sign measurement will include the following:

- Temperature
- Pulse rate
- Respiratory rate
- Systolic and diastolic blood pressure

Systolic and diastolic blood pressure and pulse measurements will be assessed while the participant is seated or supine. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs should be to be collected before blood collection for laboratory tests and before dosing with study drug.

Vital sign measurements may be performed by an MN professional.

8.5.3 Electrocardiograms

Several 12-lead ECGs will be obtained as outlined in the schedules of activities (see Section 1.3, Table 1 and Table 2) using an ECG machine that automatically calculates the following heart rate and measures: PR, QRS, QT, and QTcF. The QTc measurements will use QTcF. ECG should be repeated if clinically indicated.

When the timing of a blood sample coincides with the timing of a 12-lead ECG measurement, the ECG will be completed within 1 hour before or after the collection of the blood sample.

8.5.4 Clinical Safety Laboratory Assessments

Clinical laboratory evaluations for safety will be performed by the local laboratory. Before starting the study and throughout its duration, the investigator will provide the Sponsor (or its designee) copies of all laboratory certifications and normal ranges for all laboratory assessments to be performed by that laboratory.

Clinical laboratory evaluations will be conducted at the timepoints outlined in the schedules of activities (refer to Section 1.3, Table 1 and Table 2). In addition, all clinically significant laboratory abnormalities noted on testing will be followed by repeat testing and further investigated according to the judgment of the investigator.

If the screening visit tests are performed within 7 days prior to Day 1 of Cycle 1, clinical laboratory tests do not need to be repeated on Day 1 of Cycle 1.

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

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the schedule of activities.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study on the Adverse Event CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
- Note: For oncology trials, certain abnormal values may not qualify as adverse events.

Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the final dose of study treatment 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 or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

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

8.5.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is specified in the schedules of activities (refer to Section 1.3, Table 1 and Table 2).

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

Each participant must be carefully monitored for the development of any adverse events throughout the study from signing of the Informed Consent Form to 30 days after the final dose. See Section 8.6.1 and Appendix 3 for details on how these events should be recorded and reported. In addition, serious adverse events that are assessed as related to study drug that occur $>$30 days after the final dose also are to be reported.

Complete details on adverse event and serious adverse event monitoring are provided in Section 8.6.1.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment or the study (see Section 7.2).

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

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy) should be recorded in the Adverse Event eCRF and reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 30 days after the final dose of study treatment at the timepoints specified in the schedules of activities (see Section 1.3, Table 1 and Table 2).

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

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

8.6.2 Follow-Up of Adverse Events and Serious Adverse Events

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

8.6.3 Adverse Events During Crossover

Ongoing Grade 1 adverse events from previous therapy that worsen after crossover should be recorded and reported as a new adverse event. Further information on recording of crossover adverse events is provided in Appendix 3, Section A3–3.4.

8.6.4 Method of Detecting Adverse Events and Serious Adverse Events

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

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

8.6.5 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

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

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

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

Drug	Document
Pralsetinib	Pralsetinib Investigator's Brochure
Carboplatin	UK Summary of Product Characteristics
Cisplatin	UK Summary of Product Characteristics
Pemetrexed	EU Summary of Product Characteristics
Pembrolizumab	EU Summary of Product Characteristics
Gemcitabine	UK Summary of Product Characteristics
Paclitaxel	UK Summary of Product Characteristics
Nab-paclitaxel	EU Summary of Product Characteristics

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

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

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

8.6.6 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within treatment 14 days after the final dose of pralsetinib or according to the contraceptive requirements in the respective local labels for standard of care therapies.

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 7 days after the final dose of pralsetinib or according to the contraceptive requirements in the respective local labels for standard of care therapies.

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 2.

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

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

8.6.7 Death Events

Information on reporting of deaths is provided in Section A3–6.7.

8.6.8 Adverse Events of Special Interest and Selected Adverse Events

8.6.8.1 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware

of the event; see Section A3–4 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Appendix 3, Section A3–6.6)
- Suspected transmission of an infectious agent by a study treatment, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

8.6.8.2 Selected Adverse Events

Additional data will be collected for the following selected adverse events:

- Pneumonitis
- Pneumonia
- Hepatotoxicity
- Hypertension
- Hemorrhagic events
- Tumor lysis syndrome

8.6.9 Medical Monitors and Emergency Medical Contacts

Investigators will be provided with contact information for the Medical Monitor.
An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.7 PHARMACOKINETICS

As of protocol version 5, no new PK samples will be collected due to the Sponsor's decision to prematurely terminate the study. However, samples already collected may be analyzed.

8.8 PHARMACODYNAMICS

Pharmacodynamic biomarker assessments will not be performed in this study.

8.9 GENETICS

Genetic biomarker assessments will not be performed in this study.

8.10 BIOMARKER ASSESSMENTS

As of protocol version 5, no new biomarker blood or tissue samples will be collected due to the Sponsor's decision to prematurely terminate the study. However, biomarker samples already collected may be analyzed.

8.11 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.12 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

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

8.13 CLINICAL OUTCOME ASSESSMENTS

As of protocol version 5, participant-reported outcome data will no longer be collected due to the Sponsor's decision to prematurely terminate the study.

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

There are no additional assessments and procedures requiring separate consent or performed only at participating sites.

8.14.1 Overview of the Research Biosample Repository

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

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

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

8.14.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.14.2) will not be applicable at that site.

8.14.3 Sample Collection

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

- Leftover plasma and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, and peptides), including leftover tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the study.

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

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

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

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

8.14.4 Confidentiality

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

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

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

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

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

8.14.5 Consent to Participate in the Research Biosample Repository

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

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

8.14.6 Withdrawal from the Research Biosample Repository

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

wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

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

8.14.7 Monitoring and Oversight

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

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary objective of the study is to assess whether pralsetinib improves PFS compared with investigator’s choice platinum-containing chemotherapy regimens for patients with RET fusion–positive metastatic NSCLC.

Following the Sponsor’s decision to prematurely terminate the study, the analysis of the primary efficacy endpoint of PFS will no longer be conducted as per the original study protocol. Considering the expected lack of maturity of the data, the analysis of PFS will only be reported in a descriptive manner. No formal testing will be performed. Consequently, p-values will not be able to be claimed as statistically significant and therefore will be reported as descriptive in nature.

9.2 SAMPLE SIZE DETERMINATION

Originally, the sample size of this study was determined by the primary endpoint; therefore, the study was event driven.

Following the Sponsor’s decision to prematurely terminate the study and considering the expected lack of maturity of the data, the analysis of the primary efficacy endpoint of PFS will only be reported in a descriptive manner. Consequently, the study analysis will no longer be triggered by reaching a given number of events of interest. No formal testing will be performed for neither the primary nor for the key secondary efficacy endpoints. Accordingly, a control for the overall type I error (α) applying a gate-keeping

hierarchical sequential testing method will no longer be implemented. As a result, p-values will not be able to be claimed as statistically significant and therefore will be reported as descriptive in nature.

9.2.1 Analysis Sets

The analysis sets are defined in Table 6. For all efficacy analyses, participants will be grouped according to the treatment assigned at randomization. For safety analyses for the main treatment period, patients will be grouped according to whether any amount of experimental treatment is received, including cases in which experimental treatment was received in error. The safety analyses for the crossover treatment period will be reported separately.

Table 6 Analysis Sets

Analysis Set	Description
ITT	All randomized patients whether or not the assigned study treatment is received
Safety	All patients who receive any amount of any study drug

ITT = intent to treat;

9.3 STATISTICAL ANALYSES

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

9.3.1 General Considerations

In addition to specific analyses and presentations that are detailed in the following sections, study results will be presented by treatment arm (with total when appropriate) and summarized according to the nature of the variables:

- For continuous variables, using descriptive statistics, including the number of patients contributing to summary statistics, mean, standard deviation, median, and range as appropriate.
- For categorical variables, using the frequency and proportion of patients falling into each category, grouped by treatment arm (and total). The percentages given in these tables will be rounded and therefore may not always sum to 100%. If a missing category is not presented in the data display, only patients with non-missing values for the parameter being assessed will be included in the percentage calculation.

Time-to-event endpoints (i.e., PFS, OS, and DOR) will be estimated using Kaplan-Meier techniques. The median along with 95% CI will be provided using Brookmeyer and Crowley methodology (Brookmeyer and Crowley 1982) with a log-log transformation for constructing the confidence intervals. Rates at fixed timepoints will be derived from the Kaplan-Meier estimate and corresponding CI will be derived based on Greenwood formula (Greenwood 1926) for variance derivation and on log-log transformation applied

on the survivor function S(t) (Kalbfleisch and Prentice 1980). Unless otherwise specified, the stratified log-rank test will be performed to test the comparison between time-to-event endpoints. Stratification factors will be history of brain metastasis (yes vs. no), ECOG Performance Status (0 vs. 1), and intended use of pembrolizumab if randomized to the control arm (yes vs. no). Unless otherwise specified, the stratified HR between treatment groups along with its 95% CI will be obtained by fitting a stratified Cox model (Cox 1972), with treatment arm as a unique covariate. Stratification factors will be similar to the ones used in the stratified log-rank test as entered into the IwRS.

Categorical endpoints will be summarized by category for each treatment arm. The proportion will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method (Clopper and Pearson 1934). An estimate of the absolute difference in proportions and corresponding 95% CI using the normal approximation to the binomial distribution will be calculated and tested through the use of the stratified Cochran-Mantel-Haenszel test (Cochran 1954; Mantel and Haenszel 1959). In addition, the stratified odds ratios (Mantel-Haenszel estimator) between the treatments will be provided along with the 95% CI. The number and percentage of patients assigned to each response category (i.e., CR, PR, stable disease, progressive disease, not evaluable, and unknown) will be summarized by treatment arm along with the Clopper and Pearson two-sided 95% confidence limits.

9.3.2 Primary Endpoint

The primary objective of the study is to assess whether pralsetinib improves PFS, as assessed by investigator compared with investigator's choice of SOC platinum-containing anticancer treatment regimens for patients with RET fusion–positive metastatic NSCLC.

The population targeted is defined in the inclusion and exclusion criteria as part of the study protocol. Patients may be male or female and have pathologically confirmed, definitively diagnosed, locally advanced unresectable or metastatic NSCLC. Patients cannot have received any prior anticancer therapy for metastatic disease.

The primary endpoint, PFS, is defined as the time from randomization to the first occurrence of progression according to RECIST v1.1, as assessed by investigator, or death from any cause, whatever occurs first. Patients without disease progression or who have not died will be censored at the time of the last tumor assessment or, if no tumor assessments are performed after the baseline visit, on the date of randomization. The primary analysis of PFS will be analyzed in the intent-treat (ITT) population.

The treatment condition of interest to compare is the experimental treatment (pralsetinib) and any subsequent therapies vs. control treatment (investigator's choice platinum containing chemotherapy regimens) and any subsequent therapies, including experimental treatment. Indeed, the primary comparison of PFS will be made irrespective of premature discontinuation of randomized treatment or use of alternative

medications not permitted by the trial protocol before the occurrence of progressive disease.

Table 7 specifies assignment of event and censoring dates for the investigator-assessed-PFS analysis (i.e., specifies how dates of progression events and dates for censoring will be assigned in the primary analysis of PFS).

Table 7 Situations and Outcomes for the Primary Endpoint: Progression-Free Survival

Situation	Strategy to Handle Situation	Outcome (Date of Progression or Censoring)
Patients with no tumor assessments performed after the baseline visit	As missing data	Censored on the date of randomization
Patients without disease progression who have not died	As missing data	Censored at the time of the last tumor assessment
Progressive disease as assessed by investigator	As event of interest	Event at the date of tumor assessment at which progression was documented
Death before progressive disease	As event of interest	Event at the date of death
Start of subsequent anticancer therapy before disease progression as assessed by investigator or death	To be evaluated for progressive disease and survival.	Event or censored (i.e., the value for the variable PFS is used regardless of whether the situation occurs)
Premature discontinuation of randomized treatment before disease progression as assessed by investigator	To be evaluated for progressive disease and survival.	Event or censored (i.e., the value for the variable PFS is used regardless of whether the situation occurs)
Discontinuation or withdrawal from the study and lost to follow-up before disease progression as assessed by investigator	As missing data	Censored at the time of the last tumor assessment

PFS = progression-free survival.

The primary analysis of the study will compare the PFS distributions in the experimental (pralsetinib) and control (investigator's choice SOC platinum-containing anticancer regimens) arms, as described in Section 9.1. The treatment comparison will be performed using a one-sided, log-rank test (overall level of significance, 0.025) stratified by history of brain metastasis (present vs. absent), ECOG Performance Status (0 vs. 1) and intended use of pembrolizumab if randomized to the control arm (yes vs. no) as entered into the IwRS.

The survival distribution of -PFS will be estimated using the Kaplan-Meier method. PFS curves will be estimated for each group, considered separately, and compared

statistically using the stratified log-rank test. The Kaplan-Meier plots will display the number of patients at risk at equidistant timepoints.

Kaplan-Meier (i.e., product-limit) estimates of median PFS time will be presented by treatment arm together with two-sided 95% CIs calculated according to Brookmeyer and Crowley (Brookmeyer and Crowley 1982). Kaplan-Meier estimates of PFS probability at 12, 18, and 24 months will be estimated with corresponding two-sided 95% CIs derived using the log-log transformation according to Kalbfleisch and Prentice (1980).
The estimate of the standard error will be computed using Greenwood's formula.

The validity of the log-rank test relies on the same assumptions for censoring as validity of the Kaplan-Meier estimator of the survival curve (Bland and Altman 1998) namely, that censoring is unrelated to prognosis, the survival probabilities are the same for participants who are recruited early and late in the study, and the events that occur at the times specified.

The primary comparison of interest is the HR for PFS (i.e., estimates of the treatment effect in terms of PFS will be expressed as an HR). The HR will be estimated using a stratified Cox's proportional hazard model using the same stratification factors as the log-rank test. Each stratum will define a separate baseline hazard function, i.e., for the ith stratum the hazard function is expressed as follows:

$$hi(t) = hi0(t)\ \exp(x\beta),$$

for which hi0(t) defines the baseline hazard function for the ith stratum, x defines the treatment arm (0 = investigator's choice, 1 = pralsetinib), and β is the unknown regression parameter.

The HR for PFS will be calculated along with its 95% CI. The purpose of the two-sided 95% CI is to give an estimate of the respective treatment effect together with a comparable measure of reliability.

9.3.2.1 Sensitivity and Supplementary Analyses

Following the Sponsor's decision to prematurely terminate the study, only minimal sensitivity or supplementary analyses will be performed as listed in Table 8.

Table 8 Sensitivity and Supplementary Analyses of the Primary Endpoint: Progression-Free Survival, as Assessed by the Investigator

Analysis	Analysis Set	Variable	Definition	Comment
Sensitivity to assess the impact of stratification	ITT	PFS	As primary analysis	Unstratified log-rank and Cox model

ITT = intent to treat; PFS = progression-free survival.

9.3.2.2 Subgroup Analyses

Following the Sponsor's decision to prematurely terminate the study, subgroup analyses will not be performed.

9.3.3 Secondary Endpoints

The secondary endpoints are defined in Section 3 (see Table 4), and will be analyzed according to their type as described in Table 9.

Table 9 Planned Statistical Analyses of the Secondary Endpoints

Endpoint(s)	Type of Endpoint	Analysis Set	Summary of Measure	Supportive Analysis
ORR	Binary	ITT	• Stratified CMH test • Absolute difference (see Section 9.3.3)	— —
OS	Time to event	ITT	As primary	Analysis censoring patients at crossover
DOR	Binary	ITT (restricted to responders only)	As primary	—
DCR	Binary	ITT	As ORR	—

CBR = clinical benefit rate; CMH = Cochran-Mantel-Haenszel; DCR = disease control rate; DOR = duration of response; ITT = intent to treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival;

Safety analyses are described in Section 9.3.3.4.

9.3.3.1 Time-to-Event Endpoints (OS and DOR)

Time-to-event endpoints will be analyzed in the ITT population for OS and DOR (see Section 9.2.1).

Analyses of treatment differences of time-to-event endpoints will use the same methods as the primary endpoint PFS.

As described in Section 9.3.2, unless otherwise specified, the stratified log-rank test will be performed to test the comparison between time-to-event distributions. The stratified hazard ratio between the experimental and control groups along with its 95% confidence interval will be obtained by fitting a stratified Cox model with the treatment group variable as a unique covariate. The p-values for time-to-event endpoints are for descriptive purposes only, and there will be no multiplicity adjustment for these analyses.

The definition of OS, as specified in Table 4, is evaluating the OS benefit assuming subsequent anticancer therapies represent clinical practice, including the experimental treatment.

9.3.3.2 Binary Endpoints (ORR, DCR, and CBR)

Binary endpoints will be analyzed in the ITT-population (see Section 9.2.1).

As described in Section 9.3.1, the number and proportion of responders in each treatment arm, together with the two-sided 95% CIs with use of the Clopper-Pearson method will be produced. Treatment comparison of response will be made using stratified Cochran-Mantel-Haenszel test. The absolute difference and its CI between the treatment arms will be determined using the normal approximation to the binomial distribution.

Patients not meeting response criterion, including patients without any postbaseline tumor assessment, will be considered as non-responders.

9.3.3.3 Participant-Reported Outcomes

Following the Sponsor's decision to prematurely terminate the study, the analysis of PRO data will no longer be performed.

9.3.3.4 Safety Endpoints

Safety analyses will be performed on the safety population. Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics. The main treatment period and the crossover treatment period will be summarized separately. Adverse events with onset dates prior to the date at which the patient receives the first dose of crossover treatment will be reported in the main treatment period and adverse events occurring on or after that date will be reported in the crossover treatment period. Additionally, if there is an ongoing adverse event that has not resolved before crossover and worsens during the crossover treatment period, it will be reported in the crossover treatment period summary.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur after the first dose of study drug (i.e., treatment-emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

9.3.4 Other Analyses

9.3.4.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized by treatment arm. The reasons for study treatment discontinuation will also be tabulated. The number of patients who cross over from investigator's choice of SOC platinum-containing anticancer treatment regimens to receive pralsetinib will also be summarized. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized by treatment arm.

9.3.4.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment arm. The baseline value will be defined as the last available value recorded prior to the initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and frequencies with percentages will be presented for categorical variables.

9.3.4.3 Pharmacokinetic Analyses

Following the Sponsor's decision to prematurely terminate the study, no PK analysis will be conducted.

9.4 INTERIM ANALYSES

Following the Sponsor's decision to prematurely terminate the study, no interim analyses will be conducted. No formal testing will be performed for neither the primary nor for the key secondary efficacy endpoints. Accordingly, a control for the overall type I error (α) applying a gate-keeping hierarchical sequential testing method will no longer be implemented.

9.5 INDEPENDENT DATA MONITORING COMMITTEE

Refer to Section 4.1.5 for details regarding the iDMC for this study.

10. REFERENCES

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

TABLE OF CONTENTS

A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

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

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

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

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

The investigator will be responsible for the following:

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

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study (see definition of end of study in Section 4.3).

A1–3 INFORMED CONSENT PROCESS

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

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

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

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

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

A participant who is re-screened is not required to sign another Informed Consent Form if the re-screening occurs within 30 days from the previous Informed Consent Form signature date.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.
A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

In the event of a data security breach, appropriate mitigation measures will be implemented.

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

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

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

A1–5 ADMINISTRATIVE STRUCTURE

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

Approximately 140 sites globally will participate to enroll approximately 226 participants. Enrollment will occur through an interactive web-based response system (IwRS).

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic [PK] analyses), as specified in Section 8 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An independent Data Monitoring Committee (iDMC) will be employed to monitor and evaluate participant safety throughout the study (for details, refer to Section 4.1.5). A BICR facility will collect, store, and review imaging data.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local

regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

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

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

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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

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

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

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

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

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

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

A1–8 SOURCE DOCUMENTS

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

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

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

A1–9 STUDY AND SITE CLOSURE

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly

inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

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

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

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

A1–11 PROTOCOL DEVIATIONS

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

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory except for carcinoembryonic antigen (CEA), pharmacokinetic and biomarker assessments which will be performed at a central laboratory.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Sections 5.1 and 5.2, respectively.

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

Table A2-1 Protocol-Required Laboratory Assessments

Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells) • Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, and lactate dehydrogenase • Coagulation: INR, aPTT, and PT • Thyroid-function testing: thyroid-stimulating hormone, free T3, and free T4 • HIV serology • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test • HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test • Pregnancy test – All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) • CEA • Tissue, blood, PK plasma, and biomarker sample collection

CEA = carcinoembryonic antigen; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; PK = pharmacokinetic; T3 = triiodothyronine; T4 = thyroxine.

Investigators must document their review of each laboratory safety report.

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

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

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

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

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication
  - Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy

Events NOT Meeting the Definition of Adverse Event

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

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

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

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

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

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

- Results in death
- Is life threatening
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.
  - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.
- Results in persistent disability or incapacity
  - The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly or birth defect

- *Medically significant*:
  - Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

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

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–4 for reporting instructions).

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

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

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

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF. In addition, serious adverse events and non-serious adverse events of special interest are required to be reported immediately (i.e., no more than 24 hours after learning of the event) using the paper Clinical Trial Adverse Event/Special Situations Form (see Section A3–4 for details).

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

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

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

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

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

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

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–4 for reporting instructions), per the definition of serious adverse event in Section A3–2.

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

A3–3.3 ASSESSMENT OF CAUSALITY

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

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

The investigator will use clinical judgment to determine the relationship.

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

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

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

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

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

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

A3–3.4 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING DURING CROSSOVER

At the time of crossover, an ongoing Grade 1 adverse event, whose onset was during the therapy with the standard-of-care study drugs, that eventually worsens after crossover, should be recorded as a new adverse event in the Adverse Event eCRF.

The onset date of the new adverse event should be recorded as the date of the worsening. Its initial severity should be the one assessed at the date of worsening. The new adverse event's causality should also be re-assessed in relationship to both therapies (i.e., standard of-care study drugs and pralsetinib) received during the study.

The initial adverse event, which was ongoing at crossover time, should first be updated with an outcome of "Not recovered/Not resolved" (if the adverse event had been of a Grade 1 severity since its onset) or "Recovering/Resolving" (if its severity had decreased to Grade 1, before the crossover). When the worsened adverse event eventually resolves or reaches a definitive outcome (e.g., resolved with sequelae), both adverse events (i.e., the one that started during the therapy with standard-of-care study drugs, as well as the one that worsened after crossover) will be updated with that same definitive outcome.

If the event worsens to a serious adverse event or an adverse event of special interest, the event should also be reported to the Sponsor using the paper Clinical Trial Adverse Event/Special Situations Form within 24 hours of awareness (see Section A3–4).

A3–3.5 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.5.1 Investigator Follow-Up

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

New or updated information will be recorded in the originally completed CRF and for serious adverse events and non-serious adverse events of special interest is require to be immediately (i.e., no more than 24 hours after learning of the event) reported as well using the paper Clinical Trial Adverse Event/Special Situations Form (see Section A3–4 for details).

The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information. New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

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

During the adverse event reporting period (defined in Section 8.6.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.5.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge

summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

The primary mechanism for reporting serious adverse events and adverse events of special interest to the Sponsor will be the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators. This form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. In addition, the Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF as described in Section A3–4.

The investigator should report any new significant follow-up information as detailed in Section A3–4.1, to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information).

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

If a site receives a report of a new serious adverse event during this period from a study participant or receives updated data on a previously reported serious adverse event after the clinical database has been taken off line, the site should report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–4.

A3–4.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

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

A3–4.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until approximately 30 days after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

Instructions for reporting serious adverse events that occur more than 30 days after the final dose of study treatment are provided in Section A3–5.

A3–5 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 30 days after the final dose of study treatment), all deaths, regardless of cause, should be reported through use of the Death eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study treatment, the event should be reported by either faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or email address provided to investigators. In addition, the event should be recorded in the eCRF, if it is still available to the site.

A3–6 PROCEDURES FOR RECORDING ADVERSE EVENTS

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

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the

participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–6.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

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

A3–6.2 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

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

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

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

A3–6.3 PERSISTENT OF RECURRENT ADVERSE EVENTS

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

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–4 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

A3–6.4 ABNORMAL LABORATORY VALUES

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–6.4 for details on recording persistent adverse events).

A3–6.5 ABNORMAL VITAL SIGN VALUES

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–6.4 for details on recording persistent adverse events).

A3–6.6 ABNORMAL LIVER FUNCTION TESTS

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

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–6.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–4).

A3–6.7 DEATHS

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 8.6.1) that are attributed by the investigator solely to progression of non–small cell cancer (NSCLC) should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–4). An independent Data Monitoring Committee will monitor the frequency of deaths from all causes (see Section 4.1.4).

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

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–3.5.

A3–6.8 PREEXISTING MEDICAL CONDITIONS

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

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

A3–6.9 LACK OF EFFICACY OR WORSENING OF NSCLC

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse event. When recording an unanticipated worsening of non-small cell lung cancer on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of non-small cell lung cancer"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A3–6.10 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

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

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

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

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

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

A3–6.11 CASES OF OVERDOSE, MEDICATION ERROR, DRUG ABUSE, OR DRUG MISUSE

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
  - In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse
  - In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the special situation and the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–4). For pralsetinib, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.

- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with pralsetinib, regardless of whether they result in an adverse event, or they result in a non-serious adverse event, which is not an adverse events of special interest, should be recorded on the Adverse Event eCRF and reported via the paper Clinical Trial Adverse Event/Special Situations Form within 30 calendar days of awareness, as described below:

- Accidental overdose: Enter pralsetinib and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter Pralsetinib and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter pralsetinib and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter pralsetinib and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter Pralsetinib and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter Pralsetinib and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.

- Drug misuse that does not qualify as an overdose: Enter Pralsetinib and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter Pralsetinib and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter Pralsetinib and "participant supplied drug to third party" as the event term. Check the "Drug misuse" box.

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

A3–6.12 PARTICIPANT-REPORTED OUTCOME DATA

Adverse event reports will not be derived from participant-reported outcome (PRO) data by the Sponsor. Sites are not expected to review the PRO data for adverse events.

A3–6.13 SAFETY BIOMARKER DATA

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

Appendix 4
Contraceptive and Barrier Guidance

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A4–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 2 weeks after the final dose of pralsetinib, and according to the contraceptive requirements in the respective local labels for standard of care therapies.

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

A4–2 PREGNANCIES IN FEMALE PARTNERS OF MALE PARTICIPANTS

Male participants will be instructed through the Informed Consent Form to immediately inform the investigator if a female partner becomes pregnant during the study or within 1 week after the final dose of pralsetinib, and according contraceptive requirements in the respective local labels for standard of care therapies.

The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects

on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

A4–3 ABORTIONS

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–4).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–4). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

A4–4 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment or the female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–4).

Appendix 5
Safety Plan: Management of Identified and Potential Risks

Pralsetinib has been recently approved in the United States for the treatment of non-small lung cancer (NSCLC), and clinical development is ongoing. The safety plan for participants in this study is based on clinical experience with pralsetinib in completed and ongoing studies. The anticipated important safety risks for pralsetinib are outlined below. Refer to the Pralsetinib Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dose modification and treatment interruption or discontinuation, are provided below.

A5–1 DOSE MODIFICATIONS AND INTERRUPTIONS

A5–1.1 GENERAL GUIDANCE FOR DOSE MODIFICATIONS, INTERRUPTIONS, AND RE-ESCALATION

General dose modification guidelines for pralsetinib are summarized in Section A5–1.1.1. For details related to dose modification and management of specific pralsetinib-related adverse events, refer to Section A5–1.1.2. Guidance for pralsetinib dose interruptions is provided in Section A5–1.1.3. These guidelines should be followed by clinical Investigators; however, for an individual participant, dose interruptions, reductions, and treatment discontinuation should also be based on the clinical circumstance. Guidance for re-escalation after resolution of adverse drug reactions is provided in Section A5–1.1.4. Deviation from these guidelines must be documented and communicated to the Sponsor.

Dose modification or interruption guidelines for carboplatin, cisplatin, pemetrexed, gemcitabine, paclitaxel, and nab-paclitaxel are provided in Section A5–1.1.5 and for pembrolizumab in Section A5–1.1.5.

Comprehensive assessments of any study drug-related adverse events (adverse drug reactions) experienced by the participant will be performed throughout the study. The severity of the event, as well as clinical judgment will be utilized to determine appropriate management of the participant for any adverse event experienced while participating in this study. Adverse events are to be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0).

Any medication, including those administered for therapy of symptoms considered to be associated with study drug administration, should be reported on the appropriate Concomitant Medication page of the participant's electronic Case Report Form (eCRF). The symptoms should be reported on the Adverse Event page.

A5–1.1.1 Guidance for Pralsetinib Dose Modifications

Pralsetinib dose reductions to below 100 mg once a day (QD) are not permitted (see Table A5-1). If a participant requires dose reduction below these dose levels, study drug should be discontinued.

Table A5-1 Dose Modification Guidelines for Pralsetinib-Related Toxicity

Toxicity	Modification
Non-hematologic toxicity *(for pneumonitis, infections, tumor lysis syndrome, hemorrhagic events and hypertension, refer to Section A5–1.1.2 further below)*	
Grade 1	• No dose interruption or modification required.
Grade 2	• No dose interruption or modification required. If dose interruption is necessary, on improvement resume dosing without dose reduction.
Grade 3	• Occurrence: Hold until event is Grade ≤2 or has returned to baseline and then resume by reducing the dose by 100 mg less than the current dose. • Occurrence at 100 mg: Discontinue pralsetinib.
Grade 4	• Occurrence: Hold until event is Grade ≤2 or has returned to baseline, and then resume by reducing the dose by 100 mg less than the current dose. • If same adverse events recurs at Grade 3 or higher, discontinue pralsetinib.
Hematologic toxicity: anemia, neutropenia, and thrombocytopenia	
Grade 1 or Grade 2	• No dose interruption or modification required.
Grade 3 or 4	• Occurrence: Hold until event is Grade ≤2 or has returned to baseline, and then resume by reducing the dose by 100 mg less than the current dose. • Occurrence at 100 mg: Discontinue pralsetinib.
Hematologic toxicity: lymphopenia	
Grade 1 or 2	• No dose interruption or modification required.
Grade 3	• Occurrence: Reduce the dose by 100 mg less than the current dose. Interruption of dosing can be done based on clinical circumstances but is not required. • Occurrence at 100 mg: Discontinue pralsetinib.
Grade 4	• Occurrence: Hold until event is Grade ≤3 or has returned to baseline, and then resume by reducing the dose by 100 mg less than the current dose. • Occurrence at 100 mg: Discontinue pralsetinib.

A5–1.1.2 Dose Modification and Management of Specific Pralsetinib-Related Adverse Events

Pneumonitis

Pneumonitis, including interstitial lung disease, is a known side effect of tyrosine kinase inhibitors (TKIs), particularly TKIs used in the treatment of NSCLC and has also been observed with pralsetinib. Drug-related pneumonitis may be associated with signs and symptoms such as dyspnea, hypoxia, cough, hemoptysis, and fever as well as radiologic evidence of parenchymal or interstitial changes.

The diagnosis of pneumonitis and determination of causal relationship to the drug is often confounded by the underlying disease (especially lymphangitic carcinomatosis) and other factors, such as lung infection and radiation effect due to non-specific signs and symptoms as well as similar radiological appearance. Pneumonitis should be suspected when such signs and symptoms develop or in asymptomatic participants when a new ground glass opacity or interstitial infiltration is noted in imaging studies. If a participant is considered to have the potential diagnosis of drug-related pneumonitis, physical examination, assessment of oxygen saturation, and evaluation for infectious etiologies, and thoracentesis, bronchoscopy, or open lung biopsy should be considered to reach a diagnosis. If the causality is at least possibly related to the study drug, management of pneumonitis, including dose interruption and potentially discontinuation is required, as presented in Table A5-2.

Table A5-2 Pralsetinib Dose Modification Recommendations for Treatment-Related Pneumonitis

Toxicity Grade	Dose Modification
Grade 1	• Interrupt dosing for a minimum of 7 days. • Resume dosing without dose reduction when the pneumonitis has improved to Grade 1 or less. • If pneumonitis recurs, interrupt dosing until improves to Grade 1 or less, then resume dosing with a dose reduction of 100 mg. • If pneumonitis recurs, consider permanently discontinuing pralsetinib. Dosing interruption and dose reduction may be repeated; however, repeated dosing interruption and dose reduction are at the discretion of the Investigator and should be balanced with the need to treat the underlying disease.
Grade 2	• Interrupt dosing for a minimum of 7 days. • Resume dosing with a dose reduction of 100 mg when the pneumonitis has improved to Grade 1 or less. • If pneumonitis recurs, consider permanently discontinuing pralsetinib. Dosing interruption and dose reduction may be repeated; however, repeated dosing interruption and dose reduction are at the discretion of the Investigator and should be balanced with the need to treat the underlying disease.

Table A5-2 Pralsetinib Dose Modification Recommendations for Treatment-Related Pneumonitis (cont.)

Toxicity Grade	Dose Modification
Grade 3	• Permanently discontinue treatment, unless the investigator discusses with the Sponsor and believes the benefit–risk assessment justifies retreatment, and even then, the pneumonitis must be completely resolved, and the dose must be reduced by 100 mg less than the current dose. • If pneumonitis recurs, permanently discontinue treatment.
Grade 4	• Permanently discontinue treatment.

Infections

Infections (including opportunistic infections), some of which have been fatal, have been reported with participants treated with pralsetinib. *Some severe and fatal infections have not been preceded by neutropenia or lymphopenia. Any significant infection* should be managed with systemic antibiotics *(if appropriate)* and other supportive management. *Monitor closely for signs and symptoms of infection and treat appropriately.*

A causal relationship between pralsetinib and severe infection, including opportunistic infection, has now been established.

Regardless of investigator causality assessment, dose interruption and dose reduction and/or discontinuation should follow the guidelines in Table A5-3.

Table A5-3 Pralsetinib Dose Modification Recommendations for Infection

Toxicity Grade	*Dose Modification*
Grade 2–3	• *Interrupt dosing for a minimum of 7 days.* • *Resume dosing with dose reduction by 100 mg less than the previous dose prior to dose interruption, when the infection has improved to Grade <1 (infection completely cleared).*
Grade 4	• *Permanently discontinue pralsetinib.*

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been observed following pralsetinib treatment. Investigators should monitor electrolyte status and renal function by means of laboratory testing. Participants with TLS may require supportive care with IV fluids and correction of electrolyte imbalances.

Participants that are at risk for TLS at study entry, such as those with high tumor burden, should be well hydrated before initiation of pralsetinib and avoid dehydration during the first cycle. If TLS is suspected, investigators should manage the adverse event(s) according to standard institutional practices or accepted oncology management guidelines (Coiffier et al. 2008; Klastersky et al. 2016).

Hemorrhagic Events

In the ARROW study, hemorrhagic adverse events have very commonly been observed. Severe, including fatal, hemorrhagic adverse events, can occur in participants receiving pralsetinib.

A hemorrhagic adverse event considered possibly related to pralsetinib should be managed according to applicable standard-of-care guidelines. Pralsetinib dose interruption, reduction and/or discontinuation due to a severe related hemorrhagic adverse event will observe the following guidelines:

- Interrupt pralsetinib administration until resolution or improvement of hemorrhage to Grade 1; resume pralsetinib at a reduced dose.
- Permanently discontinue pralsetinib in the event of a life-threatening or recurrent severe hemorrhagic adverse event related to pralsetinib.

Hypertension

Treat with standard of care antihypertension therapy. Dose modifications not required if hypertension is able to be managed with standard of care antihypertensive therapy. If dose modification is necessary, use dose medication for non-hematologic toxicity, as described in Table A5-1.

A5–1.1.3 Dose Interruptions for Pralsetinib

Pralsetinib doses may be interrupted for study drug–related toxicities for up to 56 days (8 weeks). In general, if a study drug–related toxicity does not resolve to Grade ≤ 2 or has not returned to baseline after dose interruption for more than 56 days, the participant must be discontinued from study drug unless after discussion with the Medical Monitor, resumption of treatment is considered to be in the best medical interest of the participant and this is documented in writing.

Additionally, the Sponsor's Medical Monitor must be contacted if an adverse event deemed unrelated to treatment requires a dose interruption for more than 56 days; a longer recovery period may be considered in discussion with the medical monitor. If a participant resumes treatment after a dose hold of > 28 days, an unscheduled disease assessment should occur before restarting pralsetinib to assess status of disease after the dose hold.

For participants who require an interruption due to surgery or another procedure, study drugs should be discontinued 48 hours before the procedure and resumed 48 hours after the procedure is completed.

During dose interruptions, study sites should continue to observe the study schedule as planned.

A5–1.1.4 Dose Re-Escalation after Resolution of Pralsetinib Adverse Drug Reactions

Re-escalation of pralsetinib after dose modification for adverse events is discouraged. However, if in the opinion of the treating investigator re-escalation is warranted, this must be undertaken after consultation with the Sponsor. To be a candidate for re-escalation, the adverse event that led to dose modification must not have recurred and no other Grade 3 or 4 adverse events must have been observed during the preceding 28 days.

Participants may receive step-wise pralsetinib dose re-escalations up to 400 mg QD (e.g., 100 mg QD to 200 mg QD to 300 mg QD to 400 mg QD) if the above criteria continue to be met. A participant should be treated and tolerate therapy well for at least one cycle at each higher dose level before the dose is escalated again. In no circumstances should a participant receive a pralsetinib dose higher than 400 mg QD.

A5–1.1.5 Guidance for Cisplatin, Carboplatin, Pemetrexed, Paclitaxel, Nab-paclitaxel and Gemcitabine Dose Modifications

Guidance for dose modifications for adverse events thought to be related to cisplatin, carboplatin, pemetrexed, paclitaxel, nab-paclitaxel and gemcitabine should follow the guidance provided in the product label and on institutional standard of care.

A5–1.1.6 Guidance for Pembrolizumab Dose Modifications

Dose modifications for adverse events thought to be related to pembrolizumab should follow the guidance provided in the product label and institutional standard of care.

A brief (but not all inclusive) guidance for dose modifications due to immune-related adverse reactions related to pembrolizumab is provided in Table A5-4.

Table A5-4 Recommended Treatment Modifications for Pembrolizumab

Immune-Related Adverse Reactions	Severity	Treatment Modification
Pneumonitis	Grade 2	• Withhold until adverse reactions recover to Grade 1 [a] or better.
	Grade 3 or 4, or recurrent Grade 2	• Permanently discontinue.
Colitis	Grade 2 or 3	• Withhold until adverse reactions recover to Grade 1 [a] or better.
	Grade 4 or recurrent Grade 3	• Permanently discontinue.
Nephritis	Grade 2 with creatinine >1.5 to $\leq 3 \times$ ULN	• Withhold until adverse reactions recover to Grade 1 [a] or better.
	Grade ≥ 3 with creatinine $\leq 3 \times$ ULN	• Permanently discontinue.
Endocrinopathies	Symptomatic hypophysitis	• Withhold until adverse reactions recover to Grade 1 [a] or better.
	Type 1 diabetes associated with $\leq 3 \times$ ULN hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or associated with ketoacidosis	• For participants with Grade 3 or 4 endocrinopathy that improves to Grade 2 or less and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise, treatment should be discontinued.
	Hyperthyroidism Grade ≥ 3	• Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	Grade 2 with AST or ALT >3 to $5\times$ ULN or total bilirubin >1.5 to $3 \times$ ULN	• Withhold until adverse reactions recover to Grade 1 a or better.
	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 $\geq 50\%$ that lasts 1 or more weeks	• Permanently discontinue.

Table A5-4 Recommended Treatment Modifications for Pembrolizumab (cont.)

Immune-Related Adverse Reactions	Severity	Treatment Modification
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis	• Withhold until adverse reactions recover to Grade 1[a] or better.
	Grade 4 or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis	• Permanently discontinue.
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or 3)	• Withhold until adverse reactions recover to Grade 1[a] or better.
	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis	• Permanently discontinue.
	Grade 3 or 4 Guillain-Barré syndrome	• Permanently discontinue.
Infusion-related reactions	Grade 3 or 4	• Permanently discontinue.

ULN = upper limit of normal.

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v.5).

[a] If treatment-related toxicity does not resolve to Grade 1 or better within 12 weeks after last dose of pembrolizumab, or if corticosteroid dosing cannot be reduced to ≤ 10 mg/day prednisone or equivalent 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 Table A5-4.

REFERENCES

Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. Ann Oncol 2016;27(Suppl 5):v111–8.

Appendix 6
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, intravenous, or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

- Stop study treatment administration, if possible.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
- Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
- Continue to observe the participant and document observations.

Appendix 7
Eastern Cooperative Oncology Group Performance Status

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

Appendix 8
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter $<$ 10 mm or pathological lymph nodes with short axis $\geq$ 10 mm but $<$ 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a participant is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the participant at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For participants who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item

on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as

lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to <10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis <10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
  - All lymph nodes must be non-pathological in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A8-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A8-1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy.
The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Table A8-1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCES

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

Appendix 9
Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 5 (3 APRIL 2024):

As communicated to sites and Investigators in the memo sent on 23 January 2024, the Sponsor has decided to terminate the BO42864 study (AcceleRET-Lung) due to Blueprint Medicines' decision to discontinue global marketing and development of pralsetinib in all territories with the exclusion of the US and Greater China. Screening was closed on 26 January 2024 and the last patient was enrolled on 6 February 2024.

Investigators may continue to maintain patients on pralsetinib until continued access solutions are available. Participants randomized to Arm B and still receiving the standard-of-care (SOC) platinum-containing anticancer treatment regimen at the time of protocol version 5 should be withdrawn from the study promptly and treated according to the discretion of the investigator. In the event that the SOC treatment regimen used within the study is not available to the participant after withdrawal, the participant may remain in the study and continue to receive SOC treatment but must discontinue, at the latest, by the time the last patient receiving pralsetinib has discontinued from the study. Investigators will be given advanced notice of this timepoint. Crossover from standard of care (Arm B) to pralsetinib will no longer be an option.

Protocol BO42864 has been primarily amended to reflect changes to the study design, assessments, objectives and endpoints following the termination of the study. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

The following changes, aimed at reducing burden to patients and sites, have been made as a result of the Sponsor’s decision to prematurely terminate the study:

- The study schema has been updated to reflect changes to the study design (Section 1.2).
- The study period of long-term follow-up (i.e., progression-free survival [PFS] follow-up and survival follow-up) has been removed (Sections 1.3, 4.1, 4.1.4, 7.1).
- The timepoints for tumor imaging assessments have been updated to be performed as per the standard of care at the study site (Sections 1.3 and 8.4).
- Assessments that do not directly impact patient care and investigator's decision for participant to remain on treatment (i.e., patient-reported outcome [PRO] assessments, blood sample collection for pharmacokinetics, carcinoembryonic antigen, and biomarkers and tumor tissue collection at disease progression) have been removed (Sections 1.3 [Tables 1 and 2], 4.1.1, 8.1, 8.7, 8.10, and 8.13; Tables 3 and 4, Sections 8.13.1, 8.13.2, 8.13.2.1, and 8.13.2.2, and

Appendices 9–11 have been deleted and subsequent tables/sections/appendices have been renumbered).

- Secondary and exploratory objectives and endpoints and statistical analysis related to PRO, pharmacokinetics, and biomarkers have been removed because the corresponding assessments will no longer be performed (Sections 3, 4.2.1, 4.2.4, 9.3.3.3, and 9.3.4.3).
- The exploratory objective to assess CNS activity has been removed (Section 3).
- Instructions for participants to take pralsetinib after sample collection and completion of pretreatment assessments have been removed as it is no longer applicable (Section 6.1.1).
- As blinded independent central review (BICR) will no longer be used in this study to confirm disease progression, all requirements for BICR confirmation of disease progression have been removed (Section 4.1.3 and 7.1) and the following changes have also been introduced:
  - The primary endpoint of PFS and secondary endpoints of overall response rate, duration of response, clinical benefit rate, and disease control rate have been revised to be assessed by the investigator instead of BICR (Sections 3, 4.1, 4.1.1, 9.1, 9.2, 9.2.1, 9.3.2, 9.3.2.1, 9.3.3, 9.3.3.1, 9.3.3.2).
  - Text has been added to specify that tumor assessment scans will no longer be collected prospectively by the Sponsor or submitted to BICR facility (Section 8.4.1.1).
  - Text related to imaging review by BICR has been removed (Section 8.4.1.1)
- Text describing the premature termination of this study and next steps for the participants has been added to inform and provide guidance to investigators (Sections 4 and 4.1.1).
- Text has been added to inform investigators that the option for participants in Arm B to crossover to Arm A has been removed (Sections 4.1.2 and 5.3). As a result, text related to the crossover process and eligibility criteria has been removed (Sections 4.1.2, 5.3, and 8.6.3).
- Text has been added to state that the independent Data Monitoring Committee will review unblinded safety data until the Sponsor is unblinded, after which the study team will be responsible for monitoring patient safety in the study (Section 4.1.5).
- The end of study definition has been updated to reflect the premature termination of the study (Section 4.3).
- The duration of participation has been updated to reflect the premature termination of the study (Section 4.4).
- A statement has been added to specify that all investigators were informed of the premature study termination on 23 January 2024 (Section 7.2).

- The planned statistical analyses have been updated to reflect that the primary endpoint will only be reported descriptively and there will be no formal testing of the primary and secondary efficacy endpoints (Sections 9.1, 9.2, 9.2.2, 9.3.3.1).
- Text has been added to specify that control of the overall type I error (α) applying a gate-keeping hierarchical sequential testing method will no longer be implemented and text related to type I error has been removed (Sections 9.2, 9.2.2, and 9.4).
- The modified intent-to-treat (mITT) BICR, mITT investigator, and pharmacokinetic analysis sets have been removed as these analysis sets are no longer applicable (Section 9.2.3).
- The text describing the Statistical Analysis Plan (SAP) has been removed because a SAP will no longer be written for the study, as there is no intention to submit the statistical methods for review to Regulatory Authorities or external scientific advisors (Section 9.3).
- All planned supplementary and sensitivity analyses related to the primary endpoint, with the exception of "sensitivity to assess the impact of stratification", have been removed because the primary endpoint will only be reported descriptively and there will be no formal testing (Section 9.3.2.1).
- The description for subgroup analyses have been removed as these subgroup analyses will no longer be performed (Section 9.3.2.2).
- Duplication of the safety analyses description has been removed (Section 9.3.3).
- Text has been added to specify that an interim analysis is no longer planned given that the study is being prematurely terminated; as a result text related to the planned interim analysis and the hierarchical testing method has been removed (Section 9.4; Sections 9.4.1, 9.4.1.1, 9.4.1.2, and 9.4.2 have been deleted).

The following changes have been made to align with Clinical Trials Regulation (CTR) requirements:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 8.6.9). Medical Monitor contact information in Section 8.6.9 has been replaced with a sentence indicating that this information will be provided separately to sites.
- The synopsis has been simplified to align with CTR and other guidelines (Section 1.1).
- A comprehensive list of investigational medicinal products and auxiliary medicinal products has been added to align with CTR requirements (Section 6 and Appendix 13).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 8.6.5).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section A1-4).

- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section A1-6).

Additional changes have been made as follows:

- Text has been modified to align with updates to the Roche Global Policy on Continued Access to Investigational Medicinal Products (Section 6.6).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 8.14.6).
- Text has been clarified to indicate that any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants (Section A1-1).

PROTOCOL AMENDMENT, VERSION 4 (28 APRIL 2022):

Protocol BO42864 has been amended to merge all the changes from the five protocol clarification letters issued to sites, merge changes from the local Irish amendment into the global amendment, align the protocol with the current version of the investigator's brochure (version 6) and clarify the study requirements for adverse event reporting and tumor assessments for participants in the crossover portion of the study. While none of the individual changes are considered substantial, the cumulative sum of changes is considered substantial. Changes to the protocol, along with a rationale for each change, are summarized below.

- Table 1 was revised as follows:
  - Changed the Survival follow up period to "every 3 months" from every 12 weeks to better reflect the annual frequency of the follow up visits.
  - Clarified tumor imaging requirements to align with the protocol requirement for brain imaging at every imaging visit.
  - Added assessment time points for Carboplatin or Cisplatin, Gemcitabine, Paclitaxel, and Nab-paclitaxel for alignment with the rest of the protocol.
  - Clarified that participants should receive their first dose of study treatment no later than 7 calendar days after randomization to allow for vitamin supplementation that is required for some of the standard of care (SOC) therapies.
  - Clarified that participants should continue with the same tumor assessment schedule in follow up until confirmation of progression by BICR in alignment with the rest of the protocol.

  - Clarified the recording period for concomitant medications and the review period for adverse events for participants receiving gemcitabine and participants receiving nab-paclitaxel to align with the dosing schedule of these SOC treatment options.
  - Clarified the order in which PROs should be completed by participants and that PRO assessments are only required at Month 3 And Month 6 posttreatment discontinuation in order to assess long term outcomes of participants following treatment.
  - Added a request to maintain hard copy originals of the PRO questionnaires as part of the participant's medical record at the site for source data verification.
  - Clarified that SOC regimens can be administered up to 4 or 6 cycles based on local guidelines to align with the language in the rest of the protocol.
  - Clarified that in exceptional cases where not safe or medically feasible in the investigator's opinion, carcinoembryonic (CEA) samples may be omitted to allow for flexibility in the collection of this non-safety related assessment in exceptional circumstances.
  - Amended the requirement for biomarker collection from Cycle 24 to Cycle 25, to align with the schedule of events allowance for participants to transition to every other cycle visits after Cycle 19.
- Table 2 was revised as follows:
  - Changed the Survival follow up period to "every 3 months" from every 12 weeks to better reflect the annual frequency of the follow up visits.
  - Clarified tumor imaging requirements to align with the protocol requirement for brain imaging at every imaging visit.
  - Amended the reporting requirements for adverse events in crossover to align with the updated protocol requirement for ongoing adverse events during crossover.
  - Clarified the order in which PROs should be completed by participants and that PRO assessments are only required at Month 3 and 6 posttreatment discontinuation in order to assess long term outcomes of participants following treatment.
  - Added a request to maintain hard copy originals of the PRO questionnaires as part of the participant's medical record at the site for source data verification.
  - Aligned the pregnancy testing footnote regarding sample requirements for pregnancy testing with the main schedule of assessments.
  - Amended the requirement for biomarker sample collection from Cycle 24 to Cycle 25 to align with the schedule of events allowance for participants to transition to every other cycle visits after Cycle 19.

- Amended the biomarker sample collection for cross-cover participants (Table 4) to align with the language in the schedule of events and amend the biomarker sample collection from Cycle 24 to Cycle 25.
- Added Study BO41932 to Section 2.3.1.2 to reflect the current clinical development of pralsetinib.
- Amended the efficacy and safety background information in Section 2.3.1.2 to reflect updated pralsetinib data from the ARROW study.
- Updated Section 2.5 to address the overlap in clinical and radiological features for pulmonary toxicity with pralsetinib and SARS-Cov-2 related interstitial pneumonia and advise investigators to use their clinical judgement when evaluating and managing participants with pulmonary symptoms.
- Added Section 2.6 to provide the COVID-19 vaccine benefit-risk assessment in line with the requirement from the Medicines and Healthcare Products Regulatory Agency (MHRA).
- Amended Section 4.1.2 to clarify that participants who consider participating in the crossover part of the study, if assessed by local assessment to have disease progression, should not discontinue treatment until progression (per RECIST v1.1) has been confirmed by BICR unless:
  - The participant experiences an adverse event that requires drug discontinuation.
  - The investigator believes that the treatment is no longer effective for the participant due to symptomatic deterioration or locally confirmed progression.
- Updated Section 4.1.2 to align with the updated protocol requirement for ongoing adverse events during crossover in Section 8.6.3 and Appendix 3. Additionally, this section was also amended to allow participants in the crossover portion of the study to discontinue disease assessments after progressive disease has been confirmed by the investigator without BICR confirmation. This update was implemented to allow investigators to discontinue participants from the crossover when the participant is not benefiting from therapy given that crossover progression is not tied to an endpoint necessitating central review.
- Revised Section 4.1.4 to require participants in follow-up to continue with the same tumor assessment schedule after study treatment discontinuation until confirmation of progression in alignment with other sections of the protocol.
- Amended Section 5, in addition to the rest of the protocol, to remove any reference to Medical Monitor approval of protocol-specific eligibility criteria from the protocol. The Principal Investigator (PI) may consult with the Medical Monitor/Sponsor for advice or clarification of any eligibility criteria and may share risk factor information pertinent to the participant, but the decision of whether a participant meets the eligibility criteria to enroll to the protocol is the responsibility of the PI. This is a clarification of the responsibilities of the Principal Investigator and the role of the Medical Monitor during eligibility to ensure optimal execution of the study.

- Amended Section 5.1 to allow for the submission of fixed and embedded cell pellets from pleural effusion for central confirmation of RET fusion if a tumor issue cannot be obtained given that RET fusion testing can be performed on this type of sample. This section was also amended to omit the requirement for the submission of a pathology report with the tumor sample for RET confirmatory testing as all of the required information is already captured in the clinical database.
- Revised the eligibility criteria in Section 5.1 to align the contraceptive methods for men with the investigator's brochure, that is, men who are not sterile, must use a condom plus an additional highly effective contraceptive method with a female partner of childbearing potential.
- Revised Table 7 to correct a misalignment with the study treatment formulations, unit dose strengths, and storage conditions and to clarify the carboplatin dose for participants with squamous NSCLC when used in combination with pembrolizumab and paclitaxel/nab-paclitaxel.
- Revised Section 6.1.1 to clarify the pralsetinib administration instructions in case of missed dose.
- Revised Section 6.1.3 to include the 7day window between randomization and timing of dose administration for Cycle 1 Day 1. The requirements for pemetrexed and paclitaxel supplementation were also updated to accommodate for the variance in SOC supplementation globally.
- Amended Section 7.1 to align with the rest of the protocol in requiring participants in follow-up to continue tumor assessments per the on-treatment tumor assessment schedule of events.
- Revised the acceptable imaging techniques in Section 8.4.1.1 to simplify the bone scan requirement at subsequent tumor assessments when clinically indicated.
- Updated section 8.10 to omit the requirement for the submission of a pathology report with the submission of a tumor sample for central confirmation as all of the required information is captured in the clinical database.
- Added Section 8.6.3 to describe adverse event criteria during crossover to allow the investigator to adequately capture and ascribe causality to ongoing adverse events that worsen in crossover after administration of pralsetinib.
- Clarified the pregnancy reporting period in section 8.6.6 to align with Appendix 4 and require study participants to inform the investigator of any pregnancy during the study and after the final dose of the study treatment based on the contraceptive periods in the respective local labels for standard of care therapies.
- Updated Section 9.3.2.1, Table 13 to included additional supplementary analysis to assess the impact of the start of new anti-cancer treatment before disease progression.
- Updated Section 9.3.3.4 to reflect the amended reporting of ongoing adverse events in crossover.

- Updated secondary Medical Monitor/Emergency Medical contact (Section 8.6.9).
- Updated data collection instructions for PRO assessments (Section 8.13.1) to reflect the update from electronic PRO collection to paper PRO collection.
- Updated Appendix 2, Table 1 to correctly reflect that all safety evaluations will be performed by the local laboratory. Only specific assessments such as pharmacokinetic and biomarker assessments require central laboratory assessments.
- Added Section A3–3.4 (Appendix 3) to describe criteria for adverse events during crossover to allow the investigator to adequately capture and ascribe causality to ongoing adverse events that worsen following crossover during administration of pralsetinib.
- Revised multiple sections in Appendix 3 to describe the mechanism for reporting serious adverse events and adverse events of special interest to the Sponsor from electronic reporting system, to align with the current mechanism for reporting of adverse events and adverse events of special interest, which is the paper Clinical Trial Adverse Event/Special Situations Form.
- Added a requirement for sites to report special situations related to pralsetinib whether they do not result in an adverse event or that result in a non-serious adverse event which is not an adverse event of special interest, to be reported to the sponsor within 30 days of awareness using the paper reporting form. This change was made to align with internal guidance
- Updated Section A4–1 and Section A4–2 (Appendix 4) to align with Section 8.6.6 to require study participants to inform the investigator of any pregnancy during the study and after the final dose of the study treatment based on the contraceptive periods in the respective local labels for standard of care therapies. This change was implemented to account for the variance in the contraceptive periods for the SOC drugs based on the regional labels.
- Amended Appendix 5 to include pralsetinib dose modification recommendations for hemorrhagic adverse events to address a request from Ireland's Health Regulatory Products Authority (HPRA).

PROTOCOL AMENDMENT, VERSION 3 (29 JANUARY 2021)

Protocol BO42864 has been amended to reflect the change to F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) as the Sponsor of this study. Roche, in collaboration with Blueprint Medicine, will be responsible for the global co-development of pralsetinib. In addition, the protocol has been revised according to the Transcelerate Common Protocol Template (CPT) format and structure. Owing to the change in protocol template wording and to align with the CPT format, some sections that were previously part of the main protocol have been moved to appendices. In addition, the study design has been modified to incorporate additional approved treatment regimens

combining immunotherapy with chemotherapy for patients with squamous cell carcinoma. Such regimens have been shown to have superior overall survival outcomes compared with the chemotherapy-alone option currently permitted in the control arm for participants with rearranged during transfection (RET) fusion–positive non–small lung cancer (NSCLC) of squamous histology (Arm B).

The sample size and statistical analysis of data for this study have been modified based on results from the Phase I/II ARROW study.

The schedules of activities have been amended, including additional assessment and change in frequency of assessments. Details are referenced in summary of changes table below.

Changes that were previously made in response to feedback from Ireland's Health Regulatory Products Authority in the Ireland-specific version (Protocol BO42864, Version 2, Ireland; date final: 15 December 2020) included the following:

- The inclusion of patients with squamous NSCLC and treatment options owing to exclusion of patients with squamous NSCLC from enrollment in the study were deleted. The removal of patients with NSCLC of squamous cell histology as a treatment option in Arm B was due to differences in standard-of-care (SOC) options in Ireland, which had to include paclitaxel or nab-paclitaxel as part of the regimen.
- Note: In this amendment, the protocol was revised to include enrollment of participants with either squamous or non-squamous NSCLC. Additionally, the choice of SOC therapies, including paclitaxel and nab-paclitaxel, has been updated to align with currently approved therapies for squamous NSCLC.
- Required female participants to be tested for pregnancy at least once a month.

  The requirement for monthly pregnancy testing has been implemented in this amendment.
- Updated drug–drug interactions (DDIs) with concomitant drugs with pralsetinib to align with the Pralsetinib Investigator's Brochure, Version 4
- DDIs have been updated in this amendment based on Pralsetinib Investigator's Brochure, Version 5.

The Summary of Changes for the Ireland-specific amendment is presented in Appendix 13.

Changes that have not previously implemented at any site are presented in the following table.

This amendment is considered to be substantial.

Appendix 9: Protocol Amendment History

Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Title page and footers	• The protocol number has been changed from Blueprint Medicine Protocol BLU-667-230 to Roche Protocol BO42864. • The Sponsor of the study has been changed from Blueprint Medicine to Roche, including the Sponsor's legal registered address. • The NCT number has been added. • Reference to Blueprint Medicine's BLU-667 has been deleted and replaced with Roche RO7499790. • The Medical Monitor's name for the study has been added. • Electronic date stamp of protocol approval has been added.	Changes have been made to reflect the change in Sponsor from Blueprint Medicine to Roche and CPT format
Approval page	The approval page has been deleted.	Approval page deleted in lieu of electronic date stamp on the title page per Roche's standard operating procedures.
Protocol Amendment Acceptance Form	The form has been added.	Per Roche's standard operating procedures
Global changes	• Reference to "investigator's choice, platinum-based chemotherapy regimens" has been changed to "investigator's choice of SOC platinum-containing anticancer treatment regimens throughout the document where instituted.	• The term investigator's choice of SOC platinum-containing anticancer treatment regimens more accurately reflects the comparator therapy that might comprise both chemotherapy and immunotherapy depending on investigator's choice.

Appendix 9: Protocol Amendment History

Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
	• Reference to patient has been changed to participant. • Reference to schedule of assessments has been changed to schedule of activities.	• Per harmonized CPT content
Synopsis	The Synopsis has been revised to reflect changes made to the protocol.	Changes made for consistency with the body of the protocol
Section 1.2, Study Schema, and Figure 1, Overall Study Design	Section 1.2 and Figure 1 have been retitled (previously, Study Diagrams and Study Design). Figure 1 was revised to reflect the following changes in study design: • Updated to reflect the reduction in overall sample size from 250 to 226 participants • Added another investigator's choice of SOC platinum-containing anticancer treatment for patients with squamous histology (pembrolizumab in combination with carboplatin, paclitaxel, or nab-paclitaxel). • Clarified to indicate that participants in Arm B may elect to cross over to receive pralsetinib treatment only after confirmation of progressive disease by BICR • Added ECOG Performance Status of 0 or 1	• Revised the sample size based on updated assumptions for accrual and dropout rates used in the determination of sample size • The addition of pembrolizumab plus paclitaxel or nab-paclitaxel was based on the Phase III KEYNOTE-407 study results, which showed the addition of pembrolizumab to standard chemotherapy of paclitaxel or nab-paclitaxel and a platinum agent resulted in significantly longer overall survival and progression-free survival than chemotherapy alone. • To accurately reflect changes to the study design • ECOG Performance Status added for completeness

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Section 1.3, Schedule of Activities, Table 1 and Table 2, Table 3 (Pralsetinib PK Sample Collection), and Table 4 (Biomarker Sample Collection)	• Section 1.3 has been retitled (previously, Schedule of Assessments). • Addition of inclusion and exclusion criteria review on Day 1 of Cycle 1 (Table 1) • Optional mobile nursing (MN) visits have been added for participants and footnote h who provide consent to Table 1 for the main treatment period and Table 2 for the crossover treatment period. MN assessments include vital signs, adverse event reporting, concomitant medications, hematologic, physical examination, coagulation, and chemistry profile, urinalysis, CEA, thyroid-stimulating hormone, free T4 and free T3, and PK and plasma biomarker assessments. • Assessment of CEA (Table 1 only), thyroid-stimulating hormone, free T4 and free T3, hepatitis B and C virus and HIV serology added in Tables 1 and 2 and footnotes • The frequency of pregnancy testing has been updated to reflect that female participants are required to have a local serum or urine pregnancy test has to be performed as required by local regulations (at least monthly).	• Per Roche's model document structure • Clarification that inclusion and exclusion review should occur before the administration of the first dose of study treatment to avoid enrolling ineligible participants • Optional MN added to reduce participant burden • Carcinoembryonic antigen (CEA) samples added to monitor cancer treatment, including response to therapy and recurrence, and for correlation of CEA with cell free DNA and circulating tumor DNA, as an early measure of tumor progression • Change implemented based on health authority feedback • Clarification of coagulation parameters • TSH, free T3, and free T4 added for monitoring of thyroid function, which is particularly important in participants receiving pembrolizumab • HBV, HCV and HIV serology at screening was added to align with Roche standard inclusion criteria in oncology studies • The frequency of ECG measurements updated to add ECG measurements every 12

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
	• Coagulation has been clarified to include PT, INR, and aPTT (Tables 1 and 2) • HBV, HCV, and HIV serology assessment has been added at screening visit to support the additional inclusion criteria in Section 5.1. • The frequency of 12-lead ECG measurements has been updated to include measurements every 12 weeks during the treatment period. • Multiple footnotes have been updated to provide additional details regarding assessments and procedures.	weeks while the participants are receiving treatment to better characterize the effect of pralsetinib on QTc prolongation. • Clarification of assessments and procedures
Section 1.3, Schedule of Activities, Table 1 and Table 2, Table 3 (Pralsetinib PK Sample Collection), and Table 4 (Biomarker Sample Collection) (cont.)	• The participant-reported outcome (PRO) schedule has been revised to include additional collection times at safety follow-up as well as during progression-free survival follow-up (Tables 1 and 2). • Addition of two study drugs, paclitaxel and nab-paclitaxel in the schedule of administration to align with the options in the investigator's choice of SOC platinum-containing anticancer treatment regimens for patients with squamous NSCLC. • All biomarkers have been consolidated into one row to clarify that plasma samples for	• Inclusion of additional PRO assessment timepoints will allow for more complete PRO collection • On-treatment plasma biomarker samples will be used to explore response, early progressors by analyzing changes in ctDNA (kinetics, alterations) and may help to identify high-risk participants who may need additional treatment. In addition, samples may be used to inform future combination treatments with pralsetinib. • Moved PK collection schedule from Appendix 9 to Table 3 per CPT format and clarified predose sampling requirements

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
	biomarkers which also include assessment of circulating tumor DNA (Tables 1 and 2). • Table 3, Pralsetinib Pharmacokinetic Collection Schedule: Footnote b has been added specifying that predose samples are to be collected within 2 hours prior to receiving study treatment. • Details of the biomarker schedule and samples are presented in Table 4.	• Added Table 4, Biomarker Sample Collection
Section 1.3, Schedule of Activities and Sample Collection	Moved the PK sampling collection table from Appendix 9 to Table 3, Pralsetinib Pharmacokinetic Sample Collection, and added Table 4, Biomarker Sample Collection	Per CPT structure and format
Section 2.4, Benefit–Risk Assessment	Section title revised and section updated to include impact of COVID-19 on the benefit–risk profile	Per Roche's Drug Safety's guidance
Section 3, Objectives and Endpoints, and Table 6, Objectives and Corresponding Endpoints	• Introduction describing overall aim of study added. • Section 3.2, Secondary Objectives and Endpoints, and Section 3.3, Exploratory Objectives and Endpoints, consolidated in Section 3, Table 6, Objectives and Corresponding Endpoints. • The primary, key secondary, additional secondary and exploratory objectives and corresponding endpoints definitions have been	The endpoints have been updated to reflect Roche model document wording and the addition and reprioritization of objectives and endpoints.

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
	revised and updated to reflect Roche standard language. – The objective to assess the central nervous system activity of pralsetinib has been moved from an additional secondary objective to an exploratory objective, reflecting reprioritization of endpoints. – The objectives to assess patient health-related quality of life, lung cancer symptoms and health status moved from additional secondary objectives to exploratory objectives, reflecting reprioritization of endpoints. – The objectives to correlate steady-state systemic exposure of pralsetinib with safety endpoints and anti-tumor activity moved from additional secondary objectives to exploratory objectives, reflecting reprioritization of endpoints – An exploratory objective added to characterize the pharmacokinetics of pralsetinib in a subset of participants to obtain more complete PK data. – An exploratory objective added to identify and/or evaluate predictive biomarkers, prognostic biomarkers, and pharmacodynamic biomarkers to increase the knowledge and understanding of disease biology of RET fusion–positive NSCLC.	
Section 4.1, Overall Study Design, Section 6.3, Treatment Assignment, and Section 9.4.1, General Considerations	• The definition of the brain metastasis stratification factor has been changed to now read: history of brain metastasis (yes vs. no). Reference to “at baseline” has been deleted.	• Participants with previously treated brain metastasis that are surgically excised will be included with participants with brain metastasis identified at baseline in the same stratification group, owing to prognostic

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
		differences in participants with no history of intracranial disease.
Section 4.1.1, Main Treatment Period	• Revised descriptions of Arms A and B to specify enrollment of participants with non-squamous and squamous NSCLC • Added a second investigator's SOC choice of platinum-containing anticancer regimens to include pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for participants with squamous NSCLC.	• The addition of pembrolizumab plus paclitaxel or nab-paclitaxel as a treatment option for participants with squamous NSCLC was based on the Phase III KEYNOTE-407 study results, which showed the addition of pembrolizumab to standard chemotherapy of paclitaxel or nab-paclitaxel and a platinum-based drug resulted in significantly longer OS and PFS than chemotherapy alone.
Section 4.1.2, Crossover Treatment Period	• Clarified that participants randomized to Arm B who experience disease progression: Confirmation has been changed from radiology review to blinded independent central review (BICR) during investigator's choice of SOC platinum-containing anticancer treatment regimen for eligible participants to cross over to receive pralsetinib after confirmation of their disease progression by BICR. Participants with locally determined progressive disease not confirmed by BICR will be ineligible for crossover and will continue to survival follow-up. • Added description of optional mobile nursing visits during which certain assessments may be	• Administrative clarifications • To reduce patient burden

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
	performed for consented participants at applicable sites, following Day 1 of Cycle 2 or Day 1 of crossover Cycle 1.	
Section 4.1.3, End of Treatment Period and 30 Day Follow-Up Contact	Section has been revised to reflect that a tumor biopsy with central submission of tissue is encouraged at the time of disease progression, if safe and medically feasible. The word optional has been deleted.	Administrative clarification
Section 4.1.4, Follow-Up Period	Section has been updated to require participants without confirmed progressive disease by BICR to continue PFS follow-up even after initiation of a new anticancer therapy.	To allow complete collection of PFS events
Section 4.1.5, Independent Data Monitoring Committee	Previously in Section 7, the description of the independent Data Monitoring Committee (iDMC) has been moved to the study design section of the protocol and updated, shortening the section and referring the reader to the iDMC Charter for further details.	For consistency with Roche model document wording
Section 4.2.1 Rationale for Study Population	Section added to include rationale for the target study population with RET fusion–positive NSCLC	Per CPT structure and format
Section 4.2.3, Rationale for Control Group	Section added to include rationale for addition of pembrolizumab in combination with carboplatin and paclitaxel as an SOC comparator for participants with squamous NSCLC based on previous study results.	Per CPT structure and format

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Section 4.2.4, Rationale for Biomarker Assessments	Section added.	New section has been added to align with Roche model document wording and CPT template
Section 4.4, Duration of Participation	• The section has been updated to reflect a longer study duration based on updated enrollment projections extending the time of accrual. • The long-term follow-up duration has been updated and the total number of OS events expected at the end of the study has been added.	
Section 5, Study Population	Section revised incorporating the change in participant enrollment in Arms A and B from 125 participants in each arm to 113 participants in each arm.	For consistency with change in sample size
Section 5.1, Inclusion Criteria for All Participants	• Clarified language to specify the NSCLC staging as unresectable NSCLC (Stage IIIB) or metastatic NSCLC (Stage IV) per Union Internationale Contre le Cancer/American Joint Committee on Cancer staging system • Updated details regarding RET testing for central confirmation of RET fusion positivity • Inclusion criterion requiring that all participants either have an HIV negative test at screening or are on stable antiretroviral therapy with a CD4 count $\geq 200/\mu L$ and an undetectable viral load added • Clarified contraceptive requirements for male and female contraception	• To define the enrollment criteria based on updated staging definitions for NSCLC • Added for completeness • To further clarify the inclusion criteria for patients with HIV on the study • Amended to align with labeling information

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Section 5.2, Exclusion Criteria for All Participants	• Criterion regarding the presence of lung disease revised to exclude participants with a history of pneumonitis within the previous 12 months • Combined two exclusion criteria for participants with significant cardiovascular disease into one • The criterion regarding study drug hypersensitivity was revised to include pembrolizumab, paclitaxel, and nab-paclitaxel. • The exclusion criteria clarified regarding the eligibility of patients with infections, including the addition of criteria for patients with viral, bacterial or fungal infections, and participants with hepatitis B and C virus • An exclusion criterion was added to clarify that patients are not eligible for the study if they are concurrently enrolled in another clinical study	• To align with Roche standard exclusion criteria language • To align with the updated safety profile of pralsetinib • Clarification • To reflect all SOC therapy options included in the study • Added additional exclusion criteria to ensure participant safety • Per Roche's standard procedures
Section 5.3, Crossover Eligibility Criteria	Added wording to clarify that participants with locally determined progressive disease not confirmed by BICR will be ineligible for crossover	Clarification
Section 5.4, Lifestyle Considerations	Added subsections describing meals and dietary restrictions, caffeine, alcohol, and tobacco, activity, and contraception requirements	Per CPT structure

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Section 5.5, Screen Failures	Section updated to further clarify that participants may qualify for one additional re-screening opportunity (for two screenings total) and to clarify that participants do not need to be re-consented if re-screened within 30 days after previously signing the consent form.	Clarification
Section 5.5.1, Contraceptive Requirements, and Appendix 4, Contraceptive and Barrier Guidance	Wording outlining acceptable contraceptive methods deleted and moved to Section 5.4.4, Contraception Requirements, and cross reference to Section 5.1 added.	Per CPT structure and format and Roche model document wording
Section 6.1, Study Treatments Administered	• Table 7 has been amended to include paclitaxel and nab-paclitaxel comparators • Footnote b has been added to indicate the dosing regimen of paclitaxel for participants of Asian race/ethnicity.	To reflect the addition of pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel as a second option of investigator's choice of platinum-containing anticancer treatment regimen for patients with NSCLC of squamous histology
Section 6.1.1, Participants in Arm A and Participants Who Cross Over from Arm B to Receive Pralsetinib	Section updated to clarify that all participants should complete a pralsetinib self-administration diary throughout their treatment period	To ensure patient compliance and for pharmacokinetic sampling
Section 6.1.2, Investigator's Choice of SOC Platinum-Containing Anticancer Treatment Regimens: For Participants in Arm B	• Amended to include the administration details for the new comparator choices for squamous NSCLC, paclitaxel and nab-paclitaxel • Clarification added to define that platinum-based chemotherapy will be administered for four or six cycles based on local guidelines, and guidelines have been added regarding switching of platinum therapy during a patient's participation in the study. In addition, instructions have been added that dose modification and	For completeness

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
	discontinuation of investigator's choice of SOC platinum-containing anticancer therapy regimens should follow product labels and institutional standards.	
Section 6.1.3, Timing of Dose Administration	Revised to include timing of dose administration details for paclitaxel and nab-paclitaxel as well as prophylaxis guidelines	For completeness
Section 6.4, Study Treatment Compliance, Section 6.5, Dose Modification, and Section 6.6, Continued Access to Study Treatment after the End of the Study	Sections added.	Per CPT structure and Roche model document wording
Section 6.8.1, Permitted Therapies	Section updated to include permitted therapies for paclitaxel and nab-paclitaxel	For completeness
Section 6.8.2, Cautionary Therapy	• Section updated for cautionary medication for participants receiving pralsetinib. • Section updated to include a statement that investigators should consult the local prescribing information when determining whether a concomitant medication can be safely administered with study treatment, and for cautionary medications related to carboplatin, cisplatin, gemcitabine, pemetrexed, paclitaxel, nab-paclitaxel, and pembrolizumab, the investigator should refer to the local prescribing	• To reflect updates in the Pralsetinib Investigator's Brochure, Version 5 • For completeness

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
	information and Summary of Product Characteristics (Package Insert).	
Section 6.8.3, Prohibited Therapy and Procedures	• Section updated for prohibited therapies for participants receiving pralsetinib. • Section updated to clarify that for participants receiving pembrolizumab any live, attenuated vaccine (e.g., FluMist®) within 4 weeks prior to randomization, and during treatment are prohibited. • Section updated to include a statement that investigators should refer to the local prescribing information and Summary of Product Characteristics (Package Insert) for prohibited therapy related to carboplatin, cisplatin, gemcitabine, pemetrexed, paclitaxel, nab-paclitaxel, and pembrolizumab.	• To reflect updates in the Pralsetinib Investigator's Brochure, Version 5 • To ensure participant safety • For completeness
Section 6.10, Overdose	Section deleted and replaced with Appendix 3, Section A3-7.11 (Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse)	Per CPT structure and revised text to align with Roche model document wording
Section 7, Discontinuation of Study Treatment and Participant Discontinuation or Withdrawal	Dose modifications, interruptions and re-escalation guidelines moved to Appendix 5 and updated with information on discontinuation of study treatment, liver chemistry stopping criteria, participant discontinuation or withdrawal from the study, and participants lost to following	Per CPT structure and format and Roche model document wording

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Section 8, Study Assessments and Procedures	• Sections re-organized to align with the Roche CPT template • Wording added to reflect that at participating sites, certain assessments might be performed by mobile nursing (MN).	• Per CPT structure and format and Roche model document wording • Optional mobile nursing added to reduce participant burden
Section 8.11, Eligibility Review and Registration	Wording added to provide more detail on the timing of the submission of tumor tissue samples to the central testing site, as well as the quality and quantity of tumor tissue required for central testing.	Added for completeness
Section 8.2, Demographic Information	Wording included clarifying that demographic information such as ethnicity and race will be collected only if permissible per local regulations	Change implemented based on health authority feedback
Section 8.4, Efficacy Assessments	• Timepoints for the collection of tumor tissue samples updated to include windows of ±7 days • Clarified requirement for routine brain scans per the schedule of activities for all study participants • Clarified requirement for bone scans for all patients with known or suspected bone metastases • Wording added to include the provision of an imaging manual • The section has been updated to clarify that central imaging will be assessed by a blinded independent central review (BICR).	• Added for completeness • Brain scans required for all patients to help assess the impact of study treatment on brain metastases • Bone scans required to better assess disease burden of disease for both response and assessment • Imaging manual added for completeness • The section has been updated to clarify that crossover is allowable only if progression is determined by blinded independent central review
Section, 8.5, Safety Assessments	• Section, 8.5, Safety Assessments	• Section, 8.5, Safety Assessments

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Section 8.6, Adverse Events, Serious Adverse Events, and Other Safety Reporting	• Section 8.6, Adverse Events, Serious Adverse Events, and Other Safety Reporting	• Section 8.6, Adverse Events, Serious Adverse Events, and Other Safety Reporting
Section 8.6.8, Medical Monitors and Emergency Medical Contacts	Section added with the Medical Monitors' emergency contact information.	Per CPT structure and format
Section 8.7, Pharmacokinetics	• Additional blood sample collection from approximately 25 patients in Arm A added • The timeline for the storage of pharmacokinetic samples updated to no later than 5 years after the final Clinical Study Report	• Included to characterize the pharmacokinetics of pralsetinib • Updated to align with Roche requirements and CPT structure and format
Section 8.10, Biomarker Assessments	A new template section added to further clarify details on biomarker sample collection	Updated to align with Roche requirements and CPT structure and format
Section 8.13, Clinical Outcome Assessments	Language added to allow for the collection of participant-reported outcome assessments by telephone call in exceptional circumstances if the patient cannot get to the site.	To reduce participant burden
Section 8.14, Additional Assessments and Procedures Requiring Separate Consent or Performed Only at Participating Sites	New section added to clarify details regarding Research Biosample Repository (RBR) and details on the approval, sample collection confidentiality, consent and withdrawal	Updated to align with Roche RBR model document wording and CPT structure and format
Section 9, Statistical Considerations	The description and section headers of the statistical methods sections were deleted and renamed from previous Section 10 and moved to Section 9.	Per CPT structure and format and revised to align with Roche model document wording

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Section 9.1, Statistical Hypotheses	A description of the statistical hypothesis assuming proportional hazards model for the primary endpoint and hypothesis testing were added.	Per Roche statistical requirements
Section 9.2, Sample Size Determination	• The description of sample size determination has been clarified and reorganized into sections by the primary endpoint (Section 9.2.1) and secondary endpoints (Section 9.2.2). • Sample size, timing of analyses, and power estimates have been updated for the primary and key secondary endpoints (Sections 9.2.1 and 9.2.2). • Assumptions for median overall survival in Arm B and the hazard ratio for overall survival have been updated (Section 9.2.2). • Table 8, Clinical Trial Simulations, Table 9, Operating Characteristics, and Table 10, Timing of Analyses, have been added.	• For clarity • Sample size, the timing of analyses and power estimates have been updated to reflect updated assumptions for accrual and drop-out rates • Assumptions for median overall survival in Arm B and the corresponding hazard ratio for overall survival have been updated to reflect the impact of crossover. • For completeness
Section 9.3, Analysis Sets	• Previously described in Section 10.2, the table has been moved and revised to specify an intent-to-treat population for the primary analysis of progression-free survival as well as for overall survival and PRO analyses. • The mITT-BICR and mITT-INV analysis sets have been added and the response-evaluable population has been deleted.	• For consistency with the intent-to-treat (ITT) principle and to allow the broader inclusion of patients, the ITT population as well as modified ITT-BICR and mITT-INV populations have been added and the modified-ITT and response-evaluable populations have been removed. The primary analysis of progression-free survival, as well as the analysis of overall survival and PRO

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
		endpoints, will be conducted in the ITT population and will include all randomized patients, regardless of whether they receive treatment or their RET fusion status was confirmed by central testing. A supplementary A supplementary analysis, excluding participants who do not have centrally confirmed RET fusions, may be conducted and is described in Table 13. • The analysis of BICR-ORR and INV-ORR will be conducted in the mITT-BICR and mITT-INV.
Section 9.4.1, General Considerations	• Previously described in Section 10.2, the description has been moved and expanded with additional details on analyses of the time-to-event timepoints, the primary endpoints. • Table 12, Situations and Outcomes for the Primary Endpoint: Progression-Free Survival, as Assessed by Blinded Independent Central Review, has been added. • Subsections added describing sensitivity and supplementary analyses, subgroup analyses, and analyses of secondary endpoints have been added, including supportive Table 13 and Table 14.	For completeness

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Section 9.4.3.2, Binary Endpoints (BIRC-ORR, BICR-DCR, and	Section added and the analysis population specified.	For completeness
BICR-CBR)	Previously in Section 10.5.3.2, the description of the analyses of PRO endpoints has been revised.	Wording added for completeness
Section 9.4.3.3, Participant Reported Outcomes	Previously in Section 10.5.5, the description of the safety analyses has been updated.	Per CPT structure and format and Roche model document. Additional details added for completeness
Section 9.4.3.4, Safety Endpoints	Previously in Section 10.5, the subsections have been reorganized to include information on summaries of conduct of study, summaries of demographics and baseline characteristics, and PK analyses.	Per CPT structure and format and Roche model document
Section 9.5.1, Planned Interim Analyses	Previously in Section 10.5.7, the section has been moved and revised to include descriptions of the planned interim analysis and stopping boundaries and probabilities to stop for efficacy at the interim or final analysis in text and	Per CPT structure and format and Roche model document
Section 9.5.2, Optional Interim Analysis	newly added Table 15.	Wording added to adapt to information that may emerge during the course of the study.
Section 12, Protocol Amendment History, and Section 12.1, Amendment 1	Section added.	Per CPT structure and format
Appendix 1, Regulatory, Ethical, and Study Oversight Considerations	Sections have been moved to Appendix 12.	Per CPT structure and format and Roche model document wording
Appendix 2, Clinical Safety Laboratory Tests	Appendix added with details (e.g., final disclosure, informed consent process, data protection, administrative structure, Sponsor's publication policy).	Per CPT structure and format

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting	Appendix added	Per CPT structure and format and Roche model document wording
Appendix 4, Contraceptive and Barrier Guidance	• Appendix added • Requirements for SOC therapies aligned with labelling language detailed in this appendix.	• Per CPT structure and format and Roche model document wording • Implemented per health authority feedback
Appendix 5, Safety Plan: Management of Identified and Potential Risks	Text removed from body of protocol to appendix and updated to include the risks of paclitaxel and nab-paclitaxel	Per CPT structure and format and Roche model document wording
Appendix 6, Anaphylaxis Precautions	Appendix added	Added as a reference document for investigators and sites
Appendix 8, Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)	Appendix added	Added as a reference document for response assessments to be performed by investigators
Appendix 9, Timepoints for Pharmacokinetic Blood Sampling	Timepoints for Pharmacokinetic Blood Sampling table deleted (now in Section 1.3, Table 3) and replaced with the European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30	Per CPT structure and format
Appendix 10, Confidentiality and Investigator Statement	Appendix has been deleted, and the participant-reported outcome assessments reordered accordingly.	Per CPT structure and format
Appendix 12, Protocol Amendment History	Appendix added	Per CPT structure and format

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Protocol Location(s)	Description of Change(s)	Rationale for Change(s)
Appendix 13, Country-Specific Requirements	The Summary of Changes has been added for the Ireland-specific protocol amendment, Version 2	Per CPT structure and format
Appendix 14, List of Prohibited Medications and Foods, and Appendix 15, Medications to Be Used with Caution	Appendices have been moved to Appendices 13 and 14 from Appendices 3 and 4, respectively, and updated.	Updated lists of prohibited medications and foods and medications with potential drug-drug interactions for alignment with Pralsetinib Investigator's Brochure, Version 5.
Appendix 16, Examples of Standard Platinum-Based Chemotherapy Labeling Information	Appendix revised to include paclitaxel and nab-paclitaxel labeling information	For completeness
Appendix 17, Abbreviations	Previously in Section 13, the table has been moved to a separate appendix.	Per CPT structure and format and revisions based on changes made to the protocol

Appendix 10 List of Prohibited Medications and Foods

Medications and food to be avoided out of concern for interaction with the study drugs:

Strong Inhibitors of CYP3A4	Strong Inducers of CYP3A4
Boceprevir	Apalutamide
Conivaptan	Carbamazepine
Danoprevir and ritonavir	Enzalutamide
Elvitegravir and ritonavir	Mitotane
Grapefruit and grapefruit juice	Phenytoin
Idelalisib	Rifampin
Indinavir and ritonavir	St. John's wort
Ketoconazole	
Nefazodone	
Ombitasvir and/or dasabuvir	
Posaconazole	
Paritaprevir and ritonavir	
Ribociclib	
Telithromycin	
Troleandomycin	
Voriconazole	
Combined P-gp and Strong CYP3A4 Inhibitors	
Clarithromycin	
Cobicistat	
Itraconazole	
Lopinavir and ritonavir	
Mifebradil	
Nelfinavir	
Ritonavir	
Saquinavir and ritonavir	
Telaprevir	
Tipranavir and ritonavir	

P-gp = P-glycoprotein.

The above list of medications is not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the internet references provided below when determining whether a certain medication strongly inhibits or induces CYP3A4 or inhibits P-glycoprotein. In addition, the investigator should contact the Medical Monitor if questions arise regarding any medications not listed above.

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2

http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix 11
Medications to Be Used with Caution

Medications to be used with caution for participants treated with pralsetinib out of concern for interaction with pralsetinib are listed in the following table.

Note: The list of medications above is not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as the internet references provided below when determining whether a certain medication is a substrate of CYPs or transporters. In addition, the investigator should contact the Medical Monitor if questions arise regarding any medications not listed in the following table.

Appendix 11: Medications to Be Used with Caution

Sensitive CYP3A4 Substrates	Sensitive CYP2C9 Substrates	Sensitive CYP2C8 Substrates	P-gp Substrates	BCRP Substrates	OATP1B1 and OATP1B3 Substrates	Sensitive OAT1 Substrates	Sensitive MATE1 and MATE2-K Substrates
Alfentanil Avanafil Buspirone Conivaptan Darifenacin darunavir Ebastine Everolimus Ibrutinib Lomitapide Lovastatin midazolam Naloxegol Nisoldipine Saquinavir Simvastatin Sirolimus Tacrolimus Tipranavir Triazolam vardenafil Budesonide dasatinib Dronedarone Eletriptan Eplerenone felodipine	Celecoxib	Repaglinide	Dabigatran etexilate Digoxin fexofenadine	Rosuvastatin Sulfasalazine	Asunaprevir Atorvastatin Bosentan Danoprevir Docetaxel Fexofenadine Glyburide Nateglinide Paclitaxel Pitavastatin Pravastatin Repaglinide Rosuvastatin Simvastatin acid	Adefovir cefaclor Ceftizoxime Famotidine Furosemide Ganciclovir Methotrexate Oseltamivir Carboxylate Penicillin G	Metformin

Appendix 11: Medications to Be Used with Caution

Sensitive CYP3A4 Substrates	Sensitive CYP2C9 Substrates	Sensitive CYP2C8 Substrates	P-gp Substrates	BCRP Substrates	OATP1B1 and OATP1B3 Substrates	Sensitive OAT1 Substrates	Sensitive MATE1 and MATE2-K Substrates
Indinavir Lurasidone Maraviroc Quetiapine Sildenafil Ticagrelor Tolvaptan							

Appendix 12
Examples of Standard Platinum-Based Chemotherapy Labeling Information

Carboplatin

U.S. prescribing information for carboplatin is available at:
https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=carboplatin

The Summary of Product Characteristics for carboplatin is available at:
https://www.medicines.org.uk/emc/product/6005/smpc

The Canadian product monograph for carboplatin is available at:
https://www.pfizer.ca/sites/g/files/g10050796/f/201901/Carboplatin_PM_E_2018-12-31.pdf

Cisplatin

U.S. prescribing information for cisplatin is available at:
https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=cisplatin

The Summary of Product Characteristics for cisplatin is available at:
https://www.medicines.org.uk/emc/product/6111/smpc

The Canadian product monograph for cisplatin is available at: https://health-products.canada.ca/dpd-bdpp/dispatch-repartition.do;jsessionid=18CB926B1CCBEB101ED1B22741A1C981#results

Pemetrexed

U.S. prescribing information for pemetrexed is available at:
https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=pemetrexed

The Summary of Product Characteristics for pemetrexed is available at:
https://www.ema.europa.eu/en/documents/product-information/alimta-epar-product-information_en.pdf

The Canadian product monograph for pemetrexed is available at:
http://pi.lilly.com/ca/alimta-ca-pm.pdf

Gemcitabine

U.S. prescribing information for gemcitabine is available at:
https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=gemcitabine

The Summary of Product Characteristics for gemcitabine is available at:
https://www.medicines.org.uk/emc/product/2490/smpc

The Canadian product monograph for gemcitabine is available at:
https://www.sandoz.ca/sites/www.sandoz.ca/files/Gemcitabine_Inj_PMe_20140814.pdf

Pembrolizumab

U.S. prescribing information for pembrolizumab is available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9333c79b-d487-4538-a9f0-71b91a02b287

The Summary of Product Characteristics for pembrolizumab is available at: https://www.ema.europa.eu/en/documents/product-information/keytruda-epar-product-information_en.pdf

The Canadian product monograph for pembrolizumab is available at: https://pdf.hres.ca/dpd_pm/00049463.PDF

Paclitaxel

U.S. prescribing information for paclitaxel is available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021660s047lbl.pdf

The Summary of Product Characteristics for paclitaxel is available at: https://www.medicines.org.uk/emc/product/3891/smpc

The Canadian product monograph for paclitaxel is available at: https://health-products.canada.ca/dpd-bdpp/dispatch-repartition.do;jsessionid=18CB926B1CCBEB101ED1B22741A1C981

Nab-Paclitaxel

U.S. prescribing information for nab-paclitaxel is available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021660s047lbl.pdf

The Summary of Product Characteristics for nab-paclitaxel is available at: https://www.ema.europa.eu/en/documents/product-information/abraxane-epar-product-information_en.pdf

The Canadian product monograph for nab-paclitaxel is available at: https://media2.celgene.com/content/uploads/sites/23/Abraxane_Product_Monograph_English_Version.pdf

Appendix 13
Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A13-1 Investigational Medicinal Product Designations for the European Economic Area and the United Kingdom

Product Name	IMP Designation	Marketing Authorization Status in EEA/UK	Used within Marketing Authorization
Pralsetinib (RO7499790)	IMP (test product)	Authorized	Yes
Carboplatin	IMP (comparator)	Authorized	Yes
Cisplatin	IMP (comparator)	Authorized	Yes
Pemetrexed	IMP (comparator)	Authorized	Yes
Pembrolizumab	IMP (comparator)	Authorized	Yes
Gemcitabine	IMP (comparator)	Authorized	Yes
Paclitaxel	IMP (comparator)	Authorized	Yes
Nab-paclitaxel	IMP (comparator)	Authorized	Yes

EEA = European Economic Area; IMP = investigational medicinal product; UK = United Kingdom.

Appendix 14
Abbreviations

Abbreviation or Term	Definition
ASCO	American Society of Clinical Oncology
AUC	area under the concentration–time curve
β-hCG	β–human chorionic gonadotropin
BICR	blinded independent central review
CBR	clinical benefit rate
CDx	companion diagnostic
CEA	carcinoembryonic antigen
CR	complete response
CNS	central nervous system
COVID-19	coronavirus disease 2019
CT	computed tomography
ctDNA	circulating tumor DNA
DCR	disease control rate
DDI	drug–drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EOT	end of treatment
ESMO	European Society for Medical Oncology
EQ-5D-5L	EuroQol 5-Dimension Questionnaire, 5-level version
FDA	(U.S.) Food and Drug Administration
F1CDx	FoundationOne companion diagnostic
FFPE	formalin-fixed, paraffin-embedded
FMI	Foundation Medicine
GHS	global health status
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HR	hazard ratio
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)

Appendix 14: Abbreviations

Abbreviation or Term	Definition
IPCW	inverse probability of censoring weighting
IRB	Institutional Review Board
ITT	intent to treat
IwRS	interactive web-based response system
mITT	modified intent to treat
MKI	multikinase inhibitor
MN	mobile nursing
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0
NGS	next-generation sequencing
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD-L1	programmed death–ligand 1
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PO	orally (by mouth)
PR	partial response
PRO	participant-reported outcome
Q3W	every 3 weeks
QD	once a day
QoL	quality of life
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
RECIST v1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RET	rearranged during transfection (oncogene)
SAP	Statistical Analysis Plan

Appendix 14: Abbreviations

Abbreviation or Term	Definition
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	standard of care
TBD	to be determined
T3	triiodothyronine
T4	thyroxine
TKI	tyrosine kinase inhibitor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

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