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JDQ443

Clinical Trial Protocol CJDQ443B12201

KontRASt-06: An open-label phase II trial evaluating the activity and safety of JDQ443 single-agent as first-line treatment for patients with locally advanced or metastatic KRAS G12C-mutated non-small cell lung cancer with a PD-L1 expression < 1% or a PD-L1 expression ≥ 1% and an STK11 co-mutation.

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Clinical Trial Protocol Template Version 5.0 dated 14-Jan-2022

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Amendment 01 (06-June-2023)

Amendment rationale

At the time of release of this amendment, the study has enrolled [redacted] participants.

The primary purpose of this amendment is summarized as follows:

- To update the inclusion criterion #8 to reduce the eligibility threshold for creatinine clearance from ≥60 mL/min to ≥45 mL/min by calculation using the Cockcroft-Gault equation. This is based on results from CJDQ443B12101 (hADME) study which showed that total radiolabeled drug/metabolites were almost exclusively excreted via feces (on average [redacted]%). JDQ443 excretion in urine was [redacted] ([redacted]%). Upon analysis of AEs reported under the AESI of 'renal toxicity' from the FIH study CJDQ443A12101 (data cut off: 28-Oct-2022), the renal safety profile appears acceptable for this patient population based on the currently available data.
- To modify the exclusion criteria #4 for CNS disease to allow more flexibility for eligibility of patients with stable brain metastasis following recent FDA guidance on eligibility criteria for brain metastasis [Cancer Clinical Trial Eligibility Criteria_Brain Metastases Guidance for Industry]) and for further clarity. As a consequence, criteria based on number of lesions and dimension is eliminated, and more details are given for definition of stable metastasis and allowed treatment.
- To increase flexibility regarding material to be submitted for biomarker analyses at pre-screening and C1D1. If a tumor block (preferred option) cannot be submitted at pre-screening, tumor sections can be provided. The fixed number of 20 tumor sections to be sent to the central laboratory has been updated to a range of 16-20 tumor sections, allowing more flexibility. Similar flexibility has been implemented at C1D1, switching from fixed 10 tumor sections to a range of 6-10 tumor sections.
- To specify that patient enrollment in China must be based on local results from tissue or blood in regards to PD-L1 expression, KRAS G12C status and STK11 mutation status (cohort B only) for the following reasons: (i) the central laboratory for these biomarker tests does not have facilities in China, (ii) samples cannot be exported outside China, (iii) and a China-based central assay with appropriate validation will not be ready until late stage of the study and will be dedicated to retrospective (post-enrollment) biomarker testing.

Changes to the protocol

- Table 1-1: FACT-GP5 endpoint moved from secondary to exploratory objective. FACT-GP5 is included as exploratory to inform internal decision-making regarding development and tolerability.
- Section 1.1: wording added to clarify that Steering committee's members can include individuals who collectively have experience and expertise in leading the conduct of clinical studies within the disease area.
- Figure 1-1: Added footnote to clarify that for Chinese patients, only local biomarker results can be used for enrollment.
- Table 1-2: Added visit window for C1D15 as it was missed in original protocol.

- Table 1-3:
  - Added footnote #1 to clarify PD-L1 expression, KRAS G12C status and STK11 mutation status (cohort B only) must be determined by local assessment in China.
  - Added footnote #4 with reference to specific sections and appendixes for the ad hoc hematological and/or biochemistry sampling required in case of toxicities.
  - Updated footnote #19 to define intensive PK sampling scheme and standard PK sampling scheme.
  - Removed "x" from EOT for Food consumption as it was inserted in error.
- Section 3.2: Removed duplicate text
- Section 4.5: updated as per new Clinical Trial Protocol template
- Section 5.1:
  - Inclusion criteria #4 modified by removing information on non-validated assay regarding local results. Nevertheless, these specifications remain available in the biomarker section as mandatory requirements.
  - Inclusion criteria # 5 modified to clarify PD-L1 expression, KRAS G12C status and STK11 mutation status (cohort B only) status must be determined by local assessment in China
  - Inclusion criteria #5 "Mandatory provision of a formalin-fixed paraffin-embedded (FFPE) tumor tissue sample with at least 20% tumor content for the central assessment of KRAS G12C, PD-L1 and STK11 mutation status for all participants, including those who have biomarker status based on local tests." has been removed. Nevertheless, these specifications remain available in the biomarker section as mandatory requirements.
  - Modified inclusion criteria #10 reducing the creatinine clearance limit for eligibility to the study from 60 mL/min to 45 mL/min, as discussed in the protocol amendment rationale section
- Section 5.2: Modified exclusion criteria #4 for CNS disease as discussed in the protocol amendment rational section.
- Section 6.2: added wording to clarify when pre-dose PK samples are collected
- Table 6-3:
  - Dose modification guidance on 'LVEF decreased' was updated to include guidance when the '*LVEF is 40% to ≤45% and decrease is <10% points from baseline*'. Also, further updates made to clarify the next steps when there is no improvement in ejection fraction even after 3 weeks of interruption of study medication.
  - Grade 1 and 2 instructions added for ECG QTc interval prolonged and vascular disorders adverse drug reactions.
  - Wording updated for rash[CCI] to indicate to treat participants per institutional practice.
- Section 8.1:
  - Added text to clarify the patient enrollment in China will be based on local assessments only

  - Added text to clarify rules for enrollment based on local biomarker results and sample collection for subsequent central analysis
  - Updated header from "Tissue requirements (all participants)" to "Sample requirements (all participants)"
  - Added wording to further detail the STK11 mutation status
- Section 8.6.1:
  - Added text to define clinical outcome assessment (COAs), patient centricity and patient reported outcomes
  - Added text to clarify back-up options allowed for ePRO collections (web and interviewer modes).
- Sections 8.7.1 and 8.7.3: Adjusted wording to fulfill Indian HA new regulations on SAE reporting
- Section 8.7.5: Added following wording to fulfill Indian HA new regulations on SAE reporting 'If more stringent, local regulations regarding reporting criteria and timelines prevail.'
- Section 8.8.1:
  - Added text to clarify PK blood collection log for participants in China vs outside of China.
  - Changed number of participants to be recruited for intensive PK to approximately 10 participants per cohort (was 10 participants prior).
  - Table 8-7 and Table 8-8: Tables modified to have the same sample number and reference ids for both cohorts A and B
- Section 8.9: Added text to clarify PD-L1 expression, KRAS G12C status and STK11 mutation status (cohort B only) must be determined by local assessment for China.
- Section 8.9.1: Language changes to allow more flexibility on additional research.
- Table 8-9: Removal of fresh tissue biopsy submission at pre-screening; implementation of a range of tumor sections to be submitted at pre-screening and C1D1 allowing more flexibility; as well as highlighting "Where available" at C1D1 for tissue submission.
- Section 9.4.4. Editorial changes made to PROs section to ensure PRO and endpoint text aligned correctly with PROs and endpoints in objectives table (Table 1-1)
- Section 10.6 Appendix 6: Updated based on updated Novartis renal safety guidelines (Drug Induced Nephrotoxicity) version 2.0 and the corresponding table 10-4 and 10-5 were updated. Following the update, the major change with respect to 'alert criteria' is the monitoring based on creatinine clearance results instead of serum creatinine levels (since creatinine clearance is preferred in evaluating renal events over serum creatinine values alone, as transient increases in serum creatinine may occur as a result of non-renal factors, such as changes in hydration status in conditions such as vomiting or dehydration as well as diet or exercise).
- Minor editorial changes (i.e., typographical errors, grammatical changes, spelling, rewording) to improve flow, accuracy/understandability, and consistency have been made throughout the protocol.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Protocol summary

1.1 Summary

Protocol Title:

KontRASt-06: An open-label phase II trial evaluating the activity and safety of JDQ443 single-agent as first-line treatment for patients with locally advanced or metastatic KRAS G12C-mutated non-small cell lung cancer with a PD-L1 expression < 1% or a PD-L1 expression ≥ 1% and an STK11 co-mutation.

Brief Title:

Study of efficacy and safety of JDQ443 single-agent as first-line treatment for patients with locally advanced or metastatic KRAS G12C- mutated non-small cell lung cancer with a PD-L1 expression < 1% or a PD-L1 expression ≥ 1% and an STK11 co-mutation.

Purpose

This study aims to evaluate the antitumor activity and safety of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors harbor a KRAS G12C mutation and have a PD-L1 expression < 1% (cohort A) or a PD-L1 expression ≥ 1% and an STK11 co-mutation (cohort B).

Study Indication /Medical Condition:

Locally advanced or metastatic KRAS G12C- mutated non-small cell lung cancer with a PD-L1 expression < 1% or a PD-L1 expression ≥ 1% and an STK11 co-mutation.

Treatment type

Drug

Study type

Interventional

Objectives and Endpoints:

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary	
• To assess the antitumor activity of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1%, regardless of STK11 mutation status (cohort A).	• Overall response rate (ORR), defined as the proportion of participants with a confirmed complete response (CR) or partial response (PR) as best overall response (BOR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by blinded independent review committee (BIRC).

Key Secondary	
• To assess the antitumor activity of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥1% and an STK11 co-mutation (cohort B).	• ORR per RECIST 1.1 by BIRC.
• To assess duration of response (DOR) in both cohorts.	• DOR, defined as the time from the first occurrence of a PR or a CR per RECIST 1.1 by BIRC to the occurrence of disease progression or death due to any cause.
Secondary	
• To assess progression-free survival (PFS) in both cohorts.	• PFS, defined as the time from the date of enrollment to the date of the first documented disease progression per RECIST 1.1 by BIRC or date of death due to any cause.
• To assess overall survival (OS) in both cohorts.	• OS, defined as the time from the date of enrollment to the date of death due to any cause.
• To assess the antitumor activity of JDQ443 single-agent in both cohorts.	• Disease control rate (DCR), defined as the proportion of participants with a BOR of confirmed CR, PR and stable disease (SD) per RECIST 1.1 by BIRC. Time to response (TTR), defined as the time from the date of enrollment to the first documented response of either CR or PR per RECIST 1.1 by BIRC.
• To assess the antitumor activity of JDQ443 single-agent in both cohorts according to local radiology assessment.	• ORR, DOR, DCR, TTR and PFS per RECIST 1.1 by local radiology assessment.
• To assess the antitumor activity of JDQ443 single-agent as first-line treatment for participants whose tumors harbor an STK11 mutation regardless of PD-L1 expression status (pooled from both cohorts).	• ORR, DOR, DCR and TTR per RECIST 1.1 by BIRC and by local radiology assessment.
• To assess PFS and OS in participants whose tumors harbor an STK11 mutation regardless of PD-L1 expression status (pooled from both cohorts).	• PFS and OS
• To characterize the safety profile of JDQ443.	• Type, frequency and severity of adverse events, changes in laboratory values, vital signs, electrocardiograms (ECGs).
• To characterize the pharmacokinetics of JDQ443 in both cohorts.	• Concentration of JDQ443 in plasma and derived PK parameters, as appropriate.
• To assess the effect of JDQ443 on patient reported lung cancer symptoms, health related quality of life, health state utility and health status.	• Time to definitive deterioration (TTDD) in the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) total score (TS), and TTDD in the physical functioning (PF) scale of the EORTC QLQ-C30 • Change from baseline to each scheduled assessment and to EOT for NSCLC-SAQ total score and for each NSCLC-SAQ items/domains. • Change from baseline to each scheduled assessment and to EOT for all EORTC QLQ-C30 domains, subscales and items

Trial Design:

This is a non-randomized, open-label, single-arm, multicenter, phase II study evaluating the antitumor activity and safety of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic KRAS G12C-mutated NSCLC (Figure 1-1).

The study will have 2 non-comparative cohorts that will recruit participants in parallel according to the following characteristics:

- **Cohort A:** participants whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1%, regardless of STK11 mutation status (N=90).
- **Cohort B:** participants whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1% and an STK11 co-mutation (N=30).

Brief Summary:

This study aims to assess the antitumor activity and safety of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1% regardless of STK11 mutation status (cohort A), or a PD-L1 expression ≥ 1% and an STK11 co-mutation (cohort B).

For this study, the term "study treatment" refers to Novartis study drug JDQ443.

The study treatment begins on Cycle 1 Day 1 (C1D1) with the first administration of JDQ443.

Study completion is defined as the earliest occurrence of one of the following:

- The last participant completes last study visit (and the assessments associated with this visit have been documented and followed-up appropriately by the Investigator), dies, withdraws consent, or is lost to follow-up, whichever comes first.]
- In the event of an early study termination decision, the date of that decision.
- Another clinical study becomes available that can continue to provide JDQ443 to study participants and all participants with ongoing treatment are transferred to that clinical study.

Treatment Duration:

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Investigator decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the participant
- Disease progression per RECIST 1.1 confirmed by BIRC. In some circumstances, participants treated with JDQ443 may be allowed to continue to receive study treatment beyond disease progression per RECIST 1.1 confirmed by BIRC (Section 6.1.4.1).
- Adverse event requiring permanent discontinuation of study treatment

- Protocol deviation that results in a significant risk to participant's safety
- Withdrawal of consent
- Study is terminated by the sponsor
- Death
- Lost to follow-up

Visit Frequency:

Study visits will occur as per Table 1-3.

Treatment of interest

The following agent will be administered to all participants as study treatment:

- JDQ443 per os (PO) 200 mg twice a day continuously.

One treatment cycle consists of 21 (±3) days.

Number of Participants:

A total of 120 participants will be enrolled in 2 separate cohorts (90 in Cohort A and 30 in Cohort B).

Key Inclusion criteria

- Histologically confirmed locally advanced (stage IIIb/IIIc not eligible for definitive chemoradiation or surgical resection with curative intent) or metastatic (stage IV) NSCLC without previous systemic treatment for metastatic disease. Prior (neo)adjuvant treatment with chemotherapy and/or immunotherapy, or prior radiotherapy administered sequentially or concomitantly with chemotherapy and/or immunotherapy for localized or locally advanced disease are accepted if the time between therapy completion and enrollment is > 12 months.
- Presence of a KRAS G12C mutation (all participants) and:
  - **Cohort A:** PD-L1 expression < 1%, regardless of STK11 mutation status
  - **Cohort B:** PD-L1 expression ≥ 1% and an STK11 co-mutation
- At least one measurable lesion per RECIST 1.1.
- ECOG performance status ≤ 1.
- Participants capable of swallowing study medication.

Key Exclusion criteria

- Participants whose tumors harbor an EGFR-sensitizing mutation and/or ALK rearrangement by local laboratory testing. Participants with other known druggable alterations will be excluded, if required by local guidelines
- Previous use of a KRAS G12C inhibitor or previous systemic treatment for metastatic NSCLC.
- A medical condition that results in increased CCI [redacted]

- Known active central nervous system (CNS) metastases and/or carcinomatous meningitis
- Participants who are taking a prohibited medication (strong CYP3A inducers) that cannot be discontinued at least seven days prior to the first dose of study treatment and for the duration of the study

Treatment Groups:

The study will have 2 non-comparative cohorts that will recruit participants in parallel according to the following characteristics:

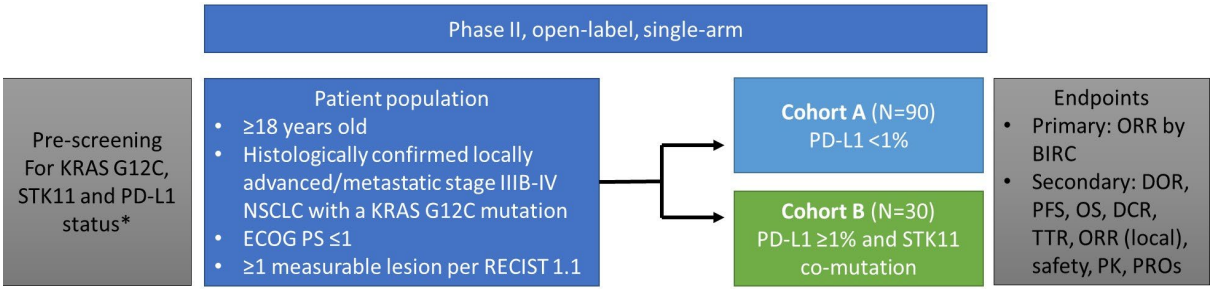
- **Cohort A:** participants whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1%, regardless of STK11 mutation status
- **Cohort B:** participants whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1% and an STK11 co-mutation

Data Monitoring/Other Committee: Yes (see Section 10.1.4 Committees Structure)

A Steering Committee (SC) will be established comprising of Investigators participating in the trial, or individuals who collectively have experience and expertise in leading the conduct of clinical studies within this disease area and Novartis representatives from the Clinical Trial Team to ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require.

1.2 Schema

Figure 1-1 Study design



*KRAS G12C and STK11 mutational status and PD-L1 expression status will be assessed locally or at the Novartis-designed central laboratory where local testing is not available for any of the applicable biomarkers (For participants in China only: central testing is not available. Only local results can be used for enrollment). Participants with local results for all applicable biomarkers may directly proceed to main screening after signing both the molecular pre-screening ICF and the main ICF.

1.3 Schedule of activities (SoA)

The SoA lists all the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment are to complete the end of treatment visit as soon as possible and attend the follow-up visits as indicated in the SoA.

Participants who discontinue from study should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse events and concomitant medications not previously reported must be recorded on the eCRF.

PRO measure(s) must be completed before any clinical assessments are performed at any given visit.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Signed informed consent must be obtained before any study specific assessments are performed, including those at molecular pre-screening and screening.

Main screening evaluations and baseline radiological tumor assessments should be performed within 28 days (and 42 days for whole body scan) of treatment start.

Laboratory assessments performed as part of the screening evaluations will not be required to be repeated on the first day of dosing (C1D1) (except for hematology/chemistry and serum pregnancy test if not done within 72 hours prior to treatment start) unless deemed clinically necessary by the Investigator and/or required as per local institutional policies.

Study treatment will begin on C1D1 with the first administration of the study treatment.

Treatment cycles are intended to last 3 weeks (21 days), but the treatment can be interrupted in order to manage toxicities according to the dose modification criteria in Section 6.5.

Please refer to Table 1-2 for allowable visits window.

Table 1-2 Allowable window for participant assessments

Visit name	Window
Screening	-28 days from the first dose of study treatment (-42 days for whole body scan)
C1D1	Within 3 days after IRT enrollment
C1D15 onwards	± 3 days
Imaging evaluations	± 7 days
ePRO (completion at home)	Within 3 days prior to the scheduled assessment
EOT	Within 7 days after stopping study treatment
30-day safety follow-up	+ 7 days
Survival	± 14 days

Table 1-3 Assessment Schedule

Period	**Screening**		**Treatment**						**Follow-up**		
Cycle			**Cycle 1**								
Visit Name	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 onwards**	**EOT**	**Safety follow-up (30 days after last administration of study treatment)**	**Efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**0**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
Molecular Pre-screening Informed Consent	X										
PD-L1 expression status per participant's record (local test result) or central test result	X										
Confirmation of KRAS G12C mutation status in tumor tissue or blood as per existing local result or central test when local is not available[1]	X										
Confirmation of STK11 mutation status in tumor tissue or blood as per existing local result or central test when local is not available (For cohort B only)[1]	X										

Period	**Screening**		**Treatment**						**Follow-up**		
Cycle			**Cycle 1**								
Visit Name	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 onwards**	**EOT**	**Safety follow-up (30 days after last administration of study treatment)**	**Efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**0**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
Tumor sample for assessment of PD-L1 expression, KRAS G12C mutation and STK11 mutation status and diagnostic development[2]	X[3]										
Blood sample for KRAS G12C/STK11 assessment and diagnostic development[2]	X[3]	X									
Collection of ALK rearrangement status, EGFR-sensitizing mutations and other known druggable alterations per local test		X									
Main Informed Consent		X									
IRT Registration	X	X									
Inclusion / Exclusion criteria		X									
Demography	X										

Period	**Screening**		**Treatment**						**Follow-up**		
Cycle			**Cycle 1**								
Visit Name	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 onwards**	**EOT**	**Safety follow-up (30 days after last administration of study treatment)**	**Efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**0**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
Diagnosis, stage and grade of cancer	X										
Medical history/current medical conditions		X									
Smoking / Vaping history		X									
Prior/concomitant medications		From 28 days prior to starting study treatment until 30 day after the last dose or start of new antineoplastic medications, whichever is sooner. After starting a new antineoplastic medications, only report concomitant medications for AEs/ SAEs suspected to be related to study treatment.									
Non-drug therapies and procedures		From 28 days prior to starting study treatment until 30 day after the last dose or start of new antineoplastic medications, whichever is sooner. After starting a new antineoplastic medications, only report non-drug therapies/procedures for AEs/ SAEs suspected to be related to study treatment.									
Prior anti-neoplastic therapies (medications, surgery, radiotherapy)		X									
IRT Enrollment			X								
Physical Examination		S	S		S		S	S	S		
ECOG performance status		X	X		X		X	X	X		
Vital Signs		X	X		X		X	X	X		
Body Height		X									
Body Weight		X	X		X		X	X	X		
Hematology[4]		X	X	X	X	X	X	X	X		

Period	**Screening**		**Treatment**						**Follow-up**		
Cycle			**Cycle 1**								
Visit Name	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 onwards**	**EOT**	**Safety follow-up (30 days after last administration of study treatment)**	**Efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**0**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
Blood Chemistry[4]		X	X	X	X	X	X	X	X		
Coagulation		X	As clinically indicated								
Hepatitis B virus (HBV) or hepatitis C virus infection, tuberculosis and/or HIV testing (if required by local regulations)		S									
Urinalysis		X	X		X		X	X	X		
Serum pregnancy test		S[5]						S			
Urine pregnancy test[6]			S		S		S				
NSCLC-SAQ[7]			Day 1 of Cycle 1, then every 7 days until cycle 3. Then on Day 1 only starting at Cycle 4 for all Cycles thereafter					X		Every 12 weeks and at disease progression per RECIST 1.1[7]	Post disease progression, every 12 weeks for a minimum of 3 timepoints
EORTC QLQ-C30[7]			Day 1 of Cycle 1, Cycle 2, Cycle 3 and then every 3 cycles thereafter					X		Every 12 weeks and at disease progression per RECIST 1.1[7]	Post disease progression, every 12 weeks for a minimum of 3 timepoints

Period	**Screening**		**Treatment**						**Follow-up**		
Cycle			**Cycle 1**								
Visit Name	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 onwards**	**EOT**	**Safety follow-up (30 days after last administration of study treatment)**	**Efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**0**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
FACT GP5[7]			Day 8 of Cycle 1, then every 7 days until cycle 3. Then on Day 1 only starting at Cycle 4 for all Cycles thereafter					X		Every 12 weeks and at disease progression per RECIST 1.1[7]	Post disease progression, every 12 weeks for a minimum of 3 timepoints
PRO CTCAE[7]			Day 1 of Cycle 1, then every 7 days until cycle 3. Then on Day 1 only starting at Cycle 4 for all Cycles thereafter					X		Every 12 weeks and at disease progression per RECIST 1.1[6]	Post disease progression, every 12 weeks for a minimum of 3 timepoints
Patient Global Impression of Severity of Symptoms-NSCLC symptoms) (PGIS-NSCLC)[7]			Day 1 of Cycle 1, then every 7 days until cycle 3. Then on Day 1 only starting at Cycle 4 for all Cycles thereafter					X		Every 12 weeks and at disease progression per RECIST 1.1[7]	Post disease progression, every 12 weeks for a minimum of 3 timepoints
EQ5D-5L[7]			Day 1 of Cycle 1, Cycle 2, Cycle 3 and then-every 3 cycles thereafter					X		Every 12 weeks and at disease progression per RECIST 1.1[7]	Post disease progression, every 12 weeks for a minimum of 3 timepoints
Blood plasma for exploratory analysis of			X	X			C3 day 1	X			

Period	**Screening**		**Treatment**						**Follow-up**		
Cycle			**Cycle 1**								
Visit Name	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 onwards**	**EOT**	**Safety follow-up (30 days after last administration of study treatment)**	**Efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**0**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
CCI [redacted] (collected before treatment administration)											
CT or MRI of chest, abdomen and pelvis		X	Every 6 weeks counting from C1D1 up to 54 weeks and every 12 weeks thereafter until disease progression (by RECIST 1.1) is confirmed by BIRC								
CT or MRI of brain		X	**If brain metastases are present at baseline:** Every 6 weeks counting from C1D1 up to 54 weeks and every 12 weeks thereafter until disease progression (by RECIST 1.1) is confirmed by BIRC. **If no brain metastases at baseline:** Every 12 weeks counting from C1D1 until disease progression (by RECIST 1.1) is confirmed by BIRC								
Whole body bone scan		X[9]	If clinically indicated								
CT scan or MRI of other metastatic sites		If clinically indicated	If positive at baseline, follow same schedule as CT/MRI of chest, abdomen and pelvis. Otherwise, if clinically indicated.								
Localized bone CT, MRI or X-Ray		X[10]	If positive at baseline, follow same schedule as CT/MRI of chest, abdomen and pelvis. Otherwise, if clinically indicated.								
Photography (for any skin lesions)		X[11]	If positive at baseline, follow same schedule as CT/MRI of chest, abdomen and pelvis. Otherwise, if clinically indicated.								
Electrocardiogram (ECG)[12]		X	X[13]	X[13]	If clinically indicated			X			
Cardiac imaging (echocardiogram or CMR)		X			X	If clinically indicated		X			
Drug administration (JDQ443)			Daily								

Period	**Screening**		**Treatment**						**Follow-up**		
Cycle			**Cycle 1**								
Visit Name	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 onwards**	**EOT**	**Safety follow-up (30 days after last administration of study treatment)**	**Efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**0**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
IRT drug dispensation			X		X		X				
IRT drug discontinuation								X			
Treatment beyond progression Informed Consent			Participants who meet the criteria outlined in Section 6.1.4.1								
Adverse Events		Continuously, from signing of main ICF until 30 days after last dose of study treatment. After starting a new antineoplastic therapy, only report AEs suspected to be related to study treatment									
Serious Adverse Events	Continuously, from signing of pre-screening ICF until 30 days after last dose of study treatment. Before signing of main ICF, only SAEs suspected to be related to a study procedure are captured. After starting a new antineoplastic therapy, only report SAEs suspected to be related to study treatment (unless otherwise specified by local law/regulations).										SAEs related to study treatment (unless otherwise specified by local law/regulations)
FFPE tumor tissue sample for exploratory biomarkers[2]			X[14]								
Newly obtained tumor biopsy (core needle biopsy)[2,15]			Optional[16]	Optional (4 to 8 hours post-dose)				Optional[17]			
Blood for cell-free DNA[2]			X	X	X		C3 day 1 and then on day 1 of every 2 cycles thereafter	X			

Period	**Screening**		**Treatment**						**Follow-up**		
Cycle			**Cycle 1**								
Visit Name	**Molecular Pre-screening**	**Screening**	**Cycle 1**		**Cycle 2**		**Cycle 3 onwards**	**EOT**	**Safety follow-up (30 days after last administration of study treatment)**	**Efficacy follow-up**	**Survival follow-up (every 12 weeks)**
Days	**0**	**-28 to -1**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
JDQ443 PK sampling[18, 19]			X	X			(C3D1, C5D1 and C7D1)				
Food consumption[20]			X	X			(C3D1, C5D1 and C7D1)				
Antineoplastic therapies since discontinuation of study treatment								X	X	X	X
Disposition assessment		X						X		X	
Survival											X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
1 For participants in China Only: KRAS G12C and/or STK11 mutation and PD-L1 status must be determined by local assessment.
2 For participants in China only: Collection type and amount may vary, conditional upon approval from local authorities (including but not limited to Human Genetic Resource Administration of China (HGRAC)).
3 Tumor and blood samples are required from all participants as a part of pre-screening. For cases where documented local results from a qualified laboratory are not available and the central test results will be used for eligibility testing based on PD-L1 expression in tissue and, KRAS G12C mutation status and/or STK11 mutation status (cohort B only) in tissue or blood and the sample must be submitted as part of pre-screening. While awaiting results, patient may proceed to main screening, however results must be received with appropriate biomarker status prior to starting treatment (Section 5.1 and Section 8.1). With documented local results for all required biomarkers, the participant may enter main screening and submit the sample prior to start of treatment (Section 8.1).
4. Additional ad hoc hematological and/or biochemistry tests may be required in case of toxicities. Refer to Section 6.5.3, Table 6-3, Section 8.5.4, Table 8-5, Section 10.5 and Section 10.6.
5 To be performed within 72 hour before the first dose
6 For women of child-bearing potential only
7 Questionnaire completed at home within 3 days of the scheduled visits/follow-up assessments or at site (prior to administration of investigational product or any other study procedure)
8 At corresponding imaging efficacy follow-up visits
9 Within 42 days prior to start of study treatment

Period	Screening		Treatment						Follow-up		
Cycle			Cycle 1								
Visit Name	Molecular Pre-screening	Screening	Cycle 1		Cycle 2		Cycle 3 onwards	EOT	Safety follow-up (30 days after last administration of study treatment)	Efficacy follow-up	Survival follow-up (every 12 weeks)
Days	0	-28 to -1	Day 1	Day 15	Day 1	Day 15	Day 1	-	-	-	-

10 Mandated for any lesions identified on the whole-body bone scan that are not visible on the chest, abdomen, and pelvis CT or MRI.
11 if clinically indicated in case of skin metastatic lesions
12 Triplicate 12 lead ECG assessments (to be recorded approximately 2 minutes apart)
13 For C1D1 and C1D15, ECGs to be collected at pre-dose and 4 hours post-dose (within 15 minutes prior to PK)
14 Mandatory where sample is available and to be requested from another institution, if necessary. Not required if tumor tissue block was submitted during pre-screening/screening for PD-L1, KRAS G12C and/or STK11 assessment or if optional, newly obtained biopsy is provided at C1D1.
15 Requires optional biopsy consent within the main ICF
16 Biopsy may be performed during screening to accommodate patient scheduling.
17 Optional: At EOT if EOT=PD or at the time of first PD prior to the initiation of new anti-cancer therapies (Table 8-9)
18 Pre-dose samples collected immediately prior to the administration of study treatment
19 For approximately 10 participants in both Cohorts (A and B) PK blood samples will be collected at time-points described in Table 8-7 (Intensive PK sampling scheme). Approximately 2 participants from this intensive PK group will be from China. For the remaining participants in each of the Cohorts (A and B), standard PK blood samples will be collected at time-points described in Table 8-8 (standard PK sampling scheme). For all participants in both groups, additional blood samples will be collected when the tumor samples are collected. Unscheduled blood samples may be collected as necessary (Refer to Table 8-7 and Table 8-8).
20 Meal date/time (start/end time) before and after JDQ443 administration should be collected on the PK collection days

2 Introduction

2.1 Study rationale

KRAS are the most prevalent mutations among patients with non-small cell lung cancer (NSCLC) (Jancík et al 2010, Scheffler et al 2019). Promising signs of antitumor activity were observed in recent studies with KRAS G12C inhibitors administered to patients with locally advanced or metastatic (advanced) NSCLC previously exposed to standard treatments such as platinum-based chemotherapy and immunotherapy Skoulidis et al 2021, Riely et al 2021). Despite these encouraging results in pretreated patients, the efficacy of KRAS G12C inhibitors in the first-line setting remains unknown.

Immunotherapy is currently an important part of the standard first-line treatment for patients with advanced NSCLC whose tumors have no targetable mutations, either administered alone or combined with platinum-based chemotherapy (Planchard et al 2018, Hanna et al 2020). Notably, prior studies showed that some patients with advanced NSCLC may derive less benefit from immunotherapy, such as those whose tumors have a programmed death-ligand 1 (PD-L1) expression <1% or an STK11 mutation (Skoulidis et al 2018, Xu et al 2019, Ricciuti et al 2021).

In the context of first-line NSCLC patients in whom a lower benefit of immunotherapy is anticipated, the present study aims primarily to evaluate the antitumor activity and safety of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation and have a PD-L1 expression <1% or a PD-L1 expression ≥ 1% and an STK11 co-mutations.

The study will have 2 non-comparative cohorts that will recruit participants in parallel according to the following characteristics:

Cohort A: participants whose tumors harbor a KRAS G12C mutation and a PD-L1 expression <1%, regardless of STK11 mutation status.

Cohort B: participants whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥1% and an STK11 co-mutation.

The sample size of cohorts A and B was determined based on the estimated frequency of the molecular profile required to meet eligibility criteria for each cohort: the prevalence of PD-L1 expression <1% is estimated around 40% in patients with KRAS G12C-mutated NSCLC, whereas STK11 co-mutations are found in around 12-15% of these patients (Skoulidis et al 2015 , Skoulidis and Heymach 2019 , Aredo et al 2019, Ricciuti et al 2021, Skoulidis et al 2021).

2.2 Background

2.2.1 Overview of non-small cell lung cancer (NSCLC) pathogenesis, epidemiology and treatment

NSCLC is the most frequent histologic subtype of lung cancer, accounting for 85% of all cases. Approximately 65% of the patients with NSCLC present with advanced or metastatic disease at diagnosis (Travis et al 2015).

Platinum-based chemotherapy has been an important component of the standard first-line treatment for patients with advanced NSCLC, although over the past 20 years treatment has substantially evolved from the use of cytotoxic chemotherapy for all patients to a hallmark of personalized therapy driven by tumor and patient characteristics (Yuan et al 2019). The identification of oncogenic drivers such as Epidermal Growth Factor Receptor (EGFR), Anaplastic Lymphoma Kinase (ALK), B-Raf proto-oncogene (BRAF), and c-ros oncogene 1 (ROS-1) in subsets of patients has allowed them to be treated according to the genetic alterations present in their tumors, dramatically improving the treatment landscape of NSCLC and the prognosis of these patients (Yuan et al 2019).

More recently, immunotherapy has been incorporated as an option for NSCLC treatment, after multiple trials that have demonstrated a positive and clinically relevant impact yielded by immune checkpoint inhibitors in the overall survival (OS) of patients with advanced NSCLC after failure to platinum-based chemotherapy, as well as in the first-line setting in combination with chemotherapy or as monotherapy for patients whose tumors express PD-L1 (Lim et al 2020, Grant et al 2021).

Notably, in patients with advanced NSCLC, the benefit of immunotherapy – in monotherapy or in combination with platinum-based chemotherapy - is associated with PD-L1 expression levels: a higher magnitude of benefit from immunotherapy is observed in patients whose tumors present higher PD-L1 expression levels (Xu et al 2019).

Due to the incorporation of targeted therapies and immunotherapy into the treatment landscape of patients with advanced NSCLC, the assessment of PD-L1 expression and the evaluation of potential driver mutations are fundamental characteristics to be considered by clinicians in order to identify the most appropriate first-line treatment option for each patient (Planchard et al 2018, Hanna et al 2020, Hanna et al 2021).

2.2.2 KRAS mutation in NSCLC

Kirsten rat sarcoma viral oncogene homologue (KRAS) is the most frequently mutated oncogene in human solid cancers, being found in around 20–25% of newly diagnosed patients with NSCLC, with a higher frequency in the adenocarcinoma subtype (Sequist et al 2011, Huang et al 2021).

The KRAS oncoprotein is a guanosine triphosphate (GTP) binding and hydrolyzing protein (GTPase) with an essential role as regulator of intracellular signaling pathways, such as the mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K) and Ras-related protein (RAL), which are involved in cell proliferation, survival and tumorigenesis (In normal cells, KRAS alternates between inactive guanosine diphosphate (GDP)-bound and active GTP-bound states (Pai et al 1989).

Following mitogenic stimulation, guanine nucleotide-exchange factors (GEF), such as son of sevenless (SOS), catalyze the activation of KRAS by mediating its GTP loading. This nucleotide exchange causes significant conformational changes in the Switch I and Switch II regions of KRAS and subsequent engagement of KRAS with its effector proteins, resulting in the activation of KRAS-driven pathways. Signaling of KRAS is terminated by GTP hydrolysis. Hereby, the weak intrinsic GTPase activity of KRAS is enhanced by interaction with GTPase-activating proteins (GAP) (Jancík et al 2010).

Oncogenic activation of KRAS in NSCLC occurs predominantly through missense mutations in codon 12, with the KRAS G12C mutation being found in approximately 13% of lung adenocarcinomas. (Campbell et al 2016, Jordan et al 2017).

Mutations of KRAS at codon 12, such as G12C, impair GAP-stimulated GTP hydrolysis. The conversion of the GTP to the GDP form of KRAS G12C is therefore very slow. Consequently, KRAS G12C is shifted to the active, GTP-bound state, thus driving oncogenic signaling (, Patricelli et al 2016).

KRAS mutations do not generally overlap with classic targetable mutations such as EGFR, ROS1, BRAF and ALK in patients with NSCLC (Sequist et al 2011, Li et al 2013). These mutations are often associated with a poor prognosis and may also be implicated in resistance to targeted therapies and chemotherapy in patients with NSCLC (Guibert et al 2016, Del Re et al 2017, Goulding et al 2020).

2.2.3 KRAS mutation as a therapeutic target in NSCLC

Several therapies are currently being investigated in clinical trials to target either KRAS mutations, the MAPK pathway or alternative pathways that communicate with MAPK and may also drive cell proliferation. Previous attempts to target KRAS mutations and block MAPK signaling have mostly not succeeded, due to feedback loops within the MAPK pathway and pathway redundancy that prevent an effective blockade of this pathway, as well as due to the cross-talk between MAPK and other pathways or alternative intracellular effectors that can become active and drive cell proliferation in the presence of MAPK blockade. Hence, new therapies that directly and specifically inhibit the oncogenic driver KRAS G12C mutation are needed (Huang et al 2021).

The identification of the first selective KRAS G12C inhibitor targeting the mutated cysteine and covalently binding to a novel allosteric pocket under the Switch II (SWII) loop region exposed exclusively in the GDP-bound state of KRAS was a major breakthrough in the efforts to target KRAS and led to the identification of similar inhibitors with properties suitable for clinical development that entered clinical trials (Ostrem et al 2013).

Sotorasib (AMG-510) - a first-in-class, highly selective, irreversible KRAS G12C inhibitor - received accelerated approval from the US FDA for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). The accelerated approval was based on the overall response rate (ORR) and duration of response (DOR) shown in the phase 2 part of CodeBreaK 100 study, which included 126 patients with locally advanced or metastatic NSCLC whose tumors had a KRAS G12C mutation and who had progressed to immunotherapy or platinum-based chemotherapy (or both). Patients received sotorasib at an oral daily dose of 960 mg until disease progression. With a median follow-up of 15.3 months, 46 patients had a confirmed response – 4 complete responses and 42 partial responses – yielding an objective response rate of 37.1%, with a median DOR of 11.1 months (Skoulidis et al 2021, Lumakras FDA label 2021). Updated data from this study with a median follow-up of 24.9 months showed an ORR of 40.7% among 172 evaluable

patients, a median duration of response of 12.3 months, median PFS of 6.3 months and median OS of 12.5 months (Dy et al 2022).

Adagrasib (MRTX-849) is another selective inhibitor of KRAS G12C that is currently in clinical development and has demonstrated promising signs of activity. In the phase I/II KRYSTAL-1 trial, 79 patients with pretreated (92% had prior treatment with immunotherapy and chemotherapy) KRAS G12C-mutated NSCLC received adagrasib 600 mg twice a day. Among the 51 patients evaluable for clinical activity, 45% (23/51) achieved a partial response (Riely et 2021).

The promising antitumor activity observed to date with KRAS G12C inhibitors in the treatment of patients with advanced NSCLC raises interest in the evaluation of this class of targeted therapies in further studies.

2.2.3.1 STK11 and KRAS G12C mutations co-occurring in NSCLC

The presence of KRAS G12C mutations has been associated with an immunosuppressive tumor microenvironment in preclinical studies. This effect can be mediated by high levels of inhibitory cytokines such as factor nuclear kappa B (NF-κβ), signal transducer and activator of transcription 3 (STAT3), interleukin 6 (IL-6), interleukin 1-β (IL-1β), as well as by a high presence of myeloid-derived suppressor cells, regulatory T cells, and M2-differentiated tumor-associated macrophages in the tumoral stroma, all of which impair antitumor immunity and facilitate tumor progression (Hamarsheh et al 2020, Cucurull et 2022). Further supporting this concept, KRAS G12C inhibitors stimulate the recruitment and activation of CD8+ T cells, dendritic cells and M1-macrophages, and thus promote a shift towards a more immune-activated tumor microenvironment in preclinical models of NSCLC (Canon et al 2019, Briere et al 2021).

STK11 is a serine-threonine kinase that regulates cellular metabolism and cell cycle, and loss of function STK11 mutations promote an immunosuppressive microenvironment as they are associated with impaired T-cell recruitment and inhibition of neutrophil function (Koyama et al 2016). STK11 mutations are found in around 5% of the patients with advanced NSCLC, being more frequent among those with KRAS G12C-mutated NSCLC - around 12-15% (Skoulidis et al 2018, Scheffler et al 2019, Shire et al 2020, Ricciuti et al 2021).

Tumors harboring both a KRAS G12C and an STK11 mutation have a gene expression profile characterized by a low expression of pro-inflammatory cytokines such as type I interferon, stimulator of interferon genes (STING), DExD/H-Box Helicase 58 (DDX58), toll-like receptor 4 (TLR4), and toll-like receptor 7 (TLR7), and this profile is associated with an immunosuppressive tumor microenvironment (Ricciuti et al 2021).

Previous studies showed that STK11 mutations are associated with a worse prognosis and predict a low benefit from immunotherapy-based treatments in patients with advanced NSCLC (Ricciuti et al 2021, Shire et al 2020). However, these mutations do not seem to impact the responsiveness to KRAS G12C inhibitors, building an interesting rationale to investigate the activity of KRAS G12C inhibitors in patients whose tumors harbor both KRAS G12C and STK11 mutations (Shire et al 2020, Ricciuti et al 2021, Riely et 2021, Skoulidis et al 2021).

Overview of JDQ443

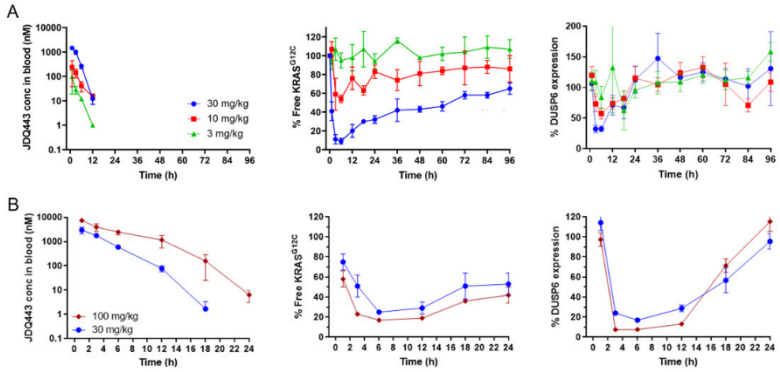
JDQ443 is a potent, selective KRAS G12C small molecule inhibitor that covalently binds to mutated Cys12, trapping KRAS G12C in the inactive GDP-bound state. Pre-clinical data indicate that JDQ443 binds to KRAS G12C with low reversible binding affinity to the RAS Switch II (SWII) pocket, inhibiting downstream cellular signaling and proliferation. Treatment with JDQ443 showed deep and sustained target occupancy resulting in anti-tumor activity in different KRAS G12C-mutated xenograft models (Brachmann et al 2021).

2.2.3.2 Non-clinical experience

2.2.3.2.1 Non-clinical pharmacology

JDQ443 selectively inhibited downstream effector protein recruitment to KRAS G12C, but not to any other RAS wild-type isoform. JDQ443 inhibited KRAS-driven oncogenic signaling and proliferation specifically in KRAS G12C-mutated cell lines, but not KRAS wild type (WT) or MEK Q56P-mutated cell lines. In KRAS G12C-mutated xenograft models, JDQ443 showed a consistent PK/PD relationship with linear exposure in blood. Upon JDQ443 treatment, free tumor KRAS G12C levels were robustly reduced in a dose-dependent manner and correlated with inhibition of tumor expression of the MAPK pathway target gene, dual-specificity phosphatase 6 (DUSP-6) (Figure 2-1).

Figure 2-1 PK/PD Relationship of JDQ443 in MIA PaCa-2 and NCI-H2122 tumor-bearing nude mice after a single oral treatment.



Nude mice bearing subcutaneous MIA PaCa-2 tumors (A) or NCI-H2122 tumors (B) were treated with a single oral dose of JDQ443 at indicated doses. Blood and tumor samples (n=3) were collected at indicated time points. Total drug concentrations in blood (left) and free KRASG12C levels in tumors (middle) were determined by LC/MS. DUSP6 expression vs control in tumors was measured by qPCR (right). A: amorphous material, solution formulation; B: crystalline material, suspension formulation.

Moreover, daily oral JDQ443 treatment resulted in dose-dependent anti-tumor activity in MIA PaCa-2 and NCI-H2122 xenograft models in mice. In MIA PaCa-2, JDQ443 produced tumor stasis at [redacted] mg/kg and tumor regression at [redacted] mg/kg, [redacted] mg/kg and [redacted] mg/kg. In NCI-H2122, JDQ443 produced weak tumor-growth inhibition at [redacted] mg/kg, a moderate tumor-growth inhibition at [redacted] mg/kg and approximately tumor stasis at [redacted] mg/kg. Likewise, a twice daily

oral treatment with JDQ443 at CCI mg/kg achieved also approximately tumor stasis in NCI-H2122, indicating that efficacy was associated with AUC (area under curve) (Figure 2-2).

Figure 2-2 Anti-tumor activity after repeated treatments of MIA PaCa-2 and NCI-H2122 tumor-bearing nude mice.

The anti-tumor activity elicited by JDQ443 in the two xenograft models MIA PaCa-2 and NCI-H2122 in mice was comparable to the one observed with AMG-510 and MRTX-849 when administered at clinically relevant doses. [JDQ443 Investigator's Brochure]

In addition, there is evidence that oncogenic KRAS signaling induces the expression of immune modulatory features (e.g., TGF-ß, interleukin-6 (IL-6) and IL-10) in tumor cells, overall imposing an immuno-suppressive tumor microenvironment (Cullis et al 2018, Van Maldegem and Downward 2020). Pre-clinical models demonstrated a substantial increase in immune cell infiltration after treatment with KRAS inhibitors (Canon et al 2019). In particular, intra-tumoral CD8+ T cell numbers increased and a shift in the tumor microenvironment was observed (e.g., macrophage polarization from M2 to M1; reduction in myeloid derived suppressor cells (Canon et al 2019,Briere et al 2021).

For further details, please refer to the [JDQ443 Investigator's Brochure].

2.2.3.2.2 Animal toxicology studies

Safety pharmacology assessments indicate that JDQ443 is not expected to cause effects on vital functions of the CNS, and the respiratory systems.

Repeat dose toxicology studies were conducted in rats and dogs.

In toxicity studies up to 4-weeks of treatment, main target organs of toxicity identified in both species were the hematopoietic system (decreases in hemoglobin, hematocrit, red blood cells, and/or reticulocytes) and the adrenal gland (cortical hypertrophy, increased or decreased vacuolation). Histopathological effects on the cardiovascular system (hypertrophy of medial smooth muscle cells in medium to large coronary arteries; increased heart rate), the kidney (tubular degeneration/regeneration) and the liver (bile duct hyperplasia) were limited to dogs.

In addition, effects on the skin/subcutis (follicular hyperplasia), the thymus (increased or decreased lymphocytes), the spleen (increased extramedullary hematopoiesis), the stomach (inflammation) and the lung (increased alveolar macrophage) were observed in rats. All findings were minimal to slight and demonstrated a partial to complete reversibility during a 4-week recovery phase.

In the 13-week dog toxicity study, additional findings were observed in the testes (seminiferous tubule degeneration), epididymis (single-cell necrosis/apoptosis, luminal cell debris) and prostate (hypoplasia). At the recovery necropsy, JDQ443-related findings had completely reversed in prostate and partially reversed in epididymis and testis. In the 13-week rat toxicity study, additional target organs of toxicity identified were the brain (mineralization, gliosis and/or necrosis), spinal cord (axonal degeneration, gliosis and/or necrosis), sciatic nerve (axonal degeneration), lung (alveolar macrophage, alveolar eosinophilic material, increased eosinophils infiltrate and/or increased pneumocyte vacuolation), parotid and mandibular salivary glands (apoptosis, vacuolation and/or mononuclear cell infiltrate; cytoplasmic alteration), skeletal muscle (myocyte degeneration, regeneration and/or mononuclear cell infiltrate) and ovary (interstitial cell degeneration, increased corpora lutea and/or follicular cyst). At recovery necropsy, microscopic findings had completely reversed in skeletal muscle and ovary. A partial recovery was observed in salivary glands. Microscopic findings were still present in spinal cord, sciatic nerve and lung at the recovery necropsy, although with an overall decreased severity when compared to the terminal euthanasia, except for the lung. Following the recovery period, mineralization was present in the brain of males, while in the brain of females mineralization and gliosis persisted and necrosis was reversed.

JDQ443 did not show evidence of a genotoxic potential in in vitro and in vivo genotoxicity studies. The rat embryofetal development study showed that JDQ443 is embryotoxic and embryolethal.

A CCI .

Further details on the risk/benefit assessment for treatment with JDQ443 are provided in Section 2.3 and detailed instructions for safety monitoring of study participants are provided in Section 6.5 and Section 8.5.

For further details, please refer to the [JDQ443 Investigator's Brochure].

2.2.3.2.3 In vitro and in vivo cardiac evaluation of JDQ443

The IC50 for JDQ443 in the hERG patch clamp is > CCI µM. Despite hERG inhibition occurring in vitro at low concentration, this potential hERG inhibition did not translate into QTc prolongation in vivo in dogs up to CCI mg. The hERG inhibition provides a safety margin of > CCI when compared to the free Cmax in patients at CCI mg b.i.d. (CCI µM). Transient increases in mean heart rate were observed in dogs at JDQ443 doses ≥ CCI mg/kg. At CCI mg/kg the mean (male and female) exposures (Cmax of CCI ng/mL and AUC0-24h of CCI ng/mL•h) were below the exposures in patients at a dose of CCI mg b.i.d. at steady state (Cmax of CCI ng/mL and AUC0-24h of CCI ng/mL•h). Additionally in the 13-week dog toxicity study echocardiogram results showed a CCI increase of left ventricular ejection fraction (LVEF) at CCI mg/kg/day; most prominent at day CCI

For further details, please refer to the [JDQ443 investigator's brochure].

2.2.3.2.4 JDQ443 absorption, metabolism, distribution and excretion

JDQ443 is a preliminary Biopharmaceutics Classification System (BCS) class 2 compound with high permeability and limited aqueous solubility, and the solubility is not pH-dependent from pH range of [redacted] to [redacted]. Following low dose intravenous administration to rat and dog, JDQ443 exhibited a rapid distribution to tissues with volume of distribution ranging from ~ [redacted] to [redacted] L/kg (Vss), high blood clearance values that exceed liver blood flow in each species, suggesting extrahepatic clearance mechanisms (CL). Terminal half-life is short ranging from [redacted] to [redacted] hours ($T_{1/2}$) in all species tested. After oral administration, the time to reach maximum drug concentrations in systemic circulation (T_{max}) occurred between [redacted] and [redacted] hours, depending on the dose levels. Dose-proportional or under-dose proportional increase of AUC_{last} was observed over the dose range tested in Good Laboratory Practice (GLP) toxicology studies. The oral bioavailability was estimated to be [redacted] % in rat. A [redacted]-fold positive food effect was observed in dog at a dose of [redacted] mg/kg.

Following oral administration of [^{14}C]JDQ443, total radiolabeled components were rapidly distributed throughout the body, with highest concentration observed in the harderian gland, pituitary gland, liver and in the intestinal wall of the colon. The radiolabeled material passed though the blood-brain barrier to a minimal extent.

[^{14}C]JDQ443 was predominantly eliminated via fecal excretion. Urinary excretion was minor with less than [redacted] % of the radioactive dose. Based on in vitro metabolism studies in cryopreserved hepatocytes across species, the apparent primary biotransformation pathway involved [redacted] at the [redacted] moiety as well as [redacted]) and [redacted]. CYP3A is the isoform mainly contributing to the oxidative metabolism. [redacted] is an active metabolite with [redacted] potency as the parent drug and was present in the GLP toxicology studies with exposure [redacted] % and [redacted] % relative to the parent exposure in rat and dog, respectively.

Based on transporter phenotyping studies, JDQ443 is likely a substrate for efflux transporters P-gp, BCRP and MRP2. However, given the high passive permeability, co-administration of inhibitors of P-gp (MDR1), MRP2 and BCRP are expected to have little impact on rate and/or extent of JDQ443 absorption.

In vitro, JDQ443 showed weak reversible inhibition of CYP2B6, 2C8, 2C9, 2C19 and 3A4 (based on midazolam) with IC50 (unbound) values lower than [redacted] µM. There is a potential risk for reversible inhibition of CYP2C8, CYP2C9 and CYP2C19 by JDQ443 in human at clinically relevant exposure. In vitro, JDQ443 showed reversible inhibition of OATP1B1, OATP1B3 and P-gp, and may interact with substrates of these transporters at the clinically relevant concentrations.

For further details, please refer to the [JDQ443 Investigator's Brochure].

2.2.3.3 Clinical Experience with JDQ443

JDQ443 is currently being evaluated as a single agent in the first in human (FIH) study CJDQ443A12101.

A data cutoff of 03-Nov-2021 was utilized to assess data from the dose escalation portion of the JDQ443 single agent arm of CJDQ443A12101 and to confirm the recommended dose of

JDQ443 single agent. A maximum tolerated dose (MTD) for JDQ443 single agent was not reached. Based on the collective PK, PK/PD, safety and efficacy data collected across the 39 patients treated with JDQ443 single agent in dose escalation, a recommended dose of 200 mg b.i.d., given continuously and with food, was selected.

For further details, please refer to the [JDQ443 Investigator's Brochure].

2.2.3.3.1 Efficacy

In the CJDQ443A12101 study, the activity of JDQ443 as a single agent was evaluated in 39 patients with KRAS G12C-mutated solid tumors who had been previously exposed to standard of care therapies, out of whom 20 had advanced NSCLC. With a data cutoff of 05-Jan-2022, responses were assessed by RECIST1.1 criteria based on investigator's assessment. Seven out of the 20 patients with NSCLC had a confirmed PR and further 2 patients had a yet unconfirmed PR (pending confirmation), leading to an overall response rate (confirmed + unconfirmed) of 45%. Among the 7 patients who were treated at the RD (200 mg b.i.d.), 4 had a PR (all confirmed), leading to an overall response rate in this group of 57%. The median duration of exposure was 15.9 weeks (range 2.0 – 27.1), with the majority of patients (70%) ongoing on treatment at time of data cutoff. The data are not sufficiently mature to make conclusions about DoR at this time, and the data will continue to mature (Tan DS et 2022).

2.2.3.3.2 Safety

In the CJDQ443A12101 study, overall 39 patients were treated across 4 dose levels: 200 mg QD (n=10), 400 mg QD (n=11), 200 mg b.i.d. (n=11) and 300 mg b.i.d. (n=7). With a data cutoff of 05-Jan-2022, the treatment related adverse events (AEs) occurring in ≥ 10% of patients across dose levels were fatigue (30.8%), nausea (17.9%), edema (15.4%), diarrhea (12.8%), vomiting (12.8%), arthralgia (10.3%) and pruritus (10.3%). Most treatment related AEs were grade 1 or 2. QTc prolongation (grade < 3) was observed in 2 patients (5.1%), whereas no heart failure or cardiac dysfunction were observed. There were CCI [redacted] A maximum tolerated dose (MTD) was not reached. Treatment related AEs leading to dose interruption occurred in 0/10 (0%), 2/11 (18.2%), 1/11(9.1%), and 4/7 (57.1%) of patients treated at 200 mg QD, 400 mg QD, 200 mg b.i.d. and 300 mg b.i.d., respectively.

2.2.3.3.3 Clinical pharmacokinetics

Following oral administration with food, JDQ443 tablets showed prolonged absorption with a median Tmax of 3 to 4 hours post dose. The geometric mean half-life was estimated to be CCI to CCI hours. No accumulation was observed following QD or b.i.d. dosing. The exposure increase (both Cmax and AUC0-24) was less than dose proportional from CCI to CCI mg at steady state for the QD dosing schedule, likely due to saturation of absorption. The AUC0-24 at CCI mg b.i.d. was > CCI % higher than the exposure of AUC0-24 at CCI mg and CCI mg QD dose levels. The geometric mean CLss/F was CCI L/h at CCI mg QD and b.i.d., and CCI L/h at CCI mg QD.

Moderate variability was observed for Cmax (geomean CV%: [redacted]% to [redacted]%) and AUCtau (geomean CV%: [redacted]% to [redacted]%).

Exposure (AUC) of active metabolite [redacted] ([redacted]) was low, accounting for [redacted] to [redacted]% and [redacted] to [redacted]% of the parent AUC following single dose and at steady state, respectively.

PK data demonstrated that at [redacted] mg b.i.d., exposure (AUC0-24) of JDQ443 was at least [redacted]-fold above the efficacious exposure required for maximum efficacy in less sensitive xenograft models. At this dose level, a >[redacted]% average KRASG12C target occupancy was predicted based on PK-PD modeling and was higher than the [redacted]% average target occupancy required for tumor regression in various xenograft models.

For further details, please refer to the [JDQ443 Investigator's Brochure].

2.2.4 Rationale to evaluate JDQ443 as first-line treatment for selected patients with NSCLC

Although KRAS G12C inhibitors have demonstrated initial signs of antitumor activity in patients with advanced NSCLC previously exposed to standard treatments - such as platinum-based chemotherapy and immunotherapy - the efficacy of KRAS G12C inhibitors in the first-line setting remains unknown and under investigation in ongoing studies (Riely et 2021, Skoulidis et al 2021, Kwan et al 2022). Hence, patients with advanced NSCLC whose tumors harbor a KRAS G12C mutation currently receive the same first-line treatment as those whose tumors have no targetable mutations. This consists in most cases of platinum-based chemotherapy combined with immunotherapy or immunotherapy alone for patients whose tumors have a PD-L1 expression ≥50% (Planchard et al 2018, Hanna et al 2020).

Approximately 40 to 50% of the patients with advanced NSCLC are not eligible to subsequent treatments after discontinuation of first-line therapy, mainly due to clinical deterioration at the moment of disease progression (Davies et al 2017). Hence, effective treatments administered at earlier lines have the potential to benefit more patients with NSCLC.

Although the incorporation of immunotherapy into the first-line setting has significantly improved the survival of patients with advanced NSCLC, previous studies have shown that a lower magnitude of benefit from immunotherapy is observed in patients whose tumors have a PD-L1 expression < 1% or an STK11 mutation: in a retrospective study that included 1,261 patients (out of whom 42.5% and 20.6% had KRAS and STK11 mutations, respectively) with advanced lung adenocarcinoma treated with immunotherapy, the presence of an STK11 mutation co-occurring with a KRAS mutation was associated with worse PFS (HR= 2.04; 95% confidence interval [CI], 1.66–2.51; p<0.0001) and OS (HR 2.09, 95% CI, 1.68–2.61; p<0.0001) (Ricciuti et al 2021). In a meta-analysis that included 15 randomized-controlled trials involving a total of 10,074 patients, Xu et al demonstrated that the magnitude of OS benefit yielded by immunotherapy added to chemotherapy was associated with PD-L1 expression levels: for PD-L1 < 1%, HR 0.60, 95% CI, 0.43-0.83; for PD-L1 1-49%, HR 0.56, 95% CI, 0.40-0.78; for PD-L1 ≥ 50%, HR 0.50, 95% CI, 0.35-0.72 (Xu et al 2019). Hence, alternatives to improve the outcomes of these 2 subgroups of patients (PD-L1 expression < 1% and STK11 mutation) who presumably benefit less from immunotherapy-based treatment are needed. In this context, the encouraging antitumor activity of KRAS G12C inhibitors in

previously treated patients with advanced NSCLC raises interest in the evaluation of these agents in the first-line setting (Skoulidis et al 2021, Riely et 2021).

2.3 Benefit/Risk assessment

The CJDQ443B12201 trial will enroll patients with advanced NSCLC with no previous systemic treatment for advanced disease whose tumors harbor a KRAS G12C mutation and either a PD-L1 expression <1% (cohort A) or a PD-L1 expression ≥1% and an STK11 co-mutation (cohort B). These 2 subgroups of patients presumably derive less benefit from immunotherapy-based treatment in the first-line setting and thus are good candidates to alternative therapeutic strategies that aim to improve their outcomes.

Based on pre-clinical toxicology findings, it is recommended that patients in clinical studies of JDQ443 are monitored for potential hematopoietic, gastrointestinal, renal, dermatologic, hepatic, adrenal, cardiac, ophthalmologic, pulmonary, central and peripheral nervous system, muscular, salivary gland and reproductive organ effects.

JDQ443 has shown CCI [redacted]. The Investigators should recommend the use of precautionary measures against CCI [redacted] to the participants during treatment with JDQ443 CCI [redacted]

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Appropriate eligibility criteria, as well as specific dose modification and discontinuation guidance, are included in this protocol.

The central tests used to determine PD-L1, KRAS G12C and/or STK11 status for enrollment (where local test results are not available) are investigational. The tests are verified to assess PD-L1 expression (<1% or ≥1%) in tumor tissue and to detect the presence of the KRAS G12C and STK11 mutations in NSCLC tumor tissue or blood samples, however they have not been fully established to identify patients who are most likely to benefit from JDQ443 or whether the benefits will outweigh any potential serious side effects or risks from the use of these tests.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring and KRAS G12C/STK11 assay monitoring.

Considering the expected antitumor activity and safety profile of JDQ443, as well as a potential low magnitude of benefit from standard first-line treatment based on immunotherapy in the study population, a favorable risk-benefit ratio is estimated for study participation.

3 Objectives, endpoints, and estimands

The study objectives are described in Table 3-1. All objectives described in the table below will be assessed in both cohorts (A and B), unless specified otherwise in the respective objective.

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the antitumor activity of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation and a PD-L1 expression <1%, regardless of STK11 mutation status (cohort A).	• Overall response rate (ORR), defined as the proportion of participants with a confirmed complete response (CR) or partial response (PR) as best overall response (BOR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by blinded independent review committee (BIRC).
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Key secondary objective To assess the antitumor activity of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥1% and an STK11 co-mutation (cohort B).	• ORR per RECIST 1.1 by BIRC.
• Key secondary objective To assess duration of response (DOR) in both cohorts.	• DOR, defined as the time from the first occurrence of a PR or a CR per RECIST 1.1 by BIRC to the occurrence of disease progression or death due to any cause.
• Secondary objective To assess progression-free survival (PFS) in both cohorts.	• PFS, defined as the time from the date of the first dose of study treatment to the date of the first documented disease progression per RECIST 1.1 by BIRC or date of death due to any cause.
• Secondary objective To assess overall survival (OS) in both cohorts.	• OS, defined as the time from the date of enrollment to the date of death due to any cause.
• Secondary objective To assess the antitumor activity of JDQ443 single-agent in both cohorts.	• Disease control rate (DCR), defined as the proportion of participants with a BOR of confirmed CR, PR and stable disease (SD) per RECIST 1.1 by BIRC. • Time to response (TTR), defined as the time from the date of enrollment to the first documented response of either CR or PR per RECIST 1.1 by BIRC.
• Secondary objective To assess the antitumor activity of JDQ443 single-agent in both cohorts according to local radiology assessment.	• ORR, DOR, DCR, TTR and PFS per RECIST 1.1 by local radiology assessment.
• Secondary objective To assess the antitumor activity of JDQ443 single-agent as first-line treatment for participants whose tumors harbor an STK11 mutation regardless of PD-L1 expression status (pooled from both cohorts).	• ORR, DOR, DCR and TTR by BIRC and local radiology assessment.
• Secondary objective To assess PFS and OS in participants whose tumors harbor an STK11 mutation regardless of PD-L1 expression status (pooled from both cohorts).	• PFS and OS
• Secondary objective To characterize the safety profile of JDQ443.	• Type, frequency and severity of adverse events, changes in laboratory values, vital signs, electrocardiograms (ECGs).

Objective(s)	Endpoint(s)
• Secondary objective To characterize the pharmacokinetics of JDQ443 in both cohorts.	• Concentration of JDQ443 in plasma and derived PK parameters, as appropriate.
• Secondary objective To assess the effect of JDQ443 on patient reported lung cancer symptoms, health related quality of life, health utility and health status	• Time to definitive deterioration (TTD) in the NSCLC-SAQ total score, and TTD in the physical functioning (PF) scale of the EORTC QLQ-C30 • Change from baseline to each scheduled assessment and to EOT for NSCLC-SAQ total score, and for each NSCLC-SAQ item/domain. • Change from baseline to each scheduled assessment and to EOT for all EORTC QLQ-C30 domains, subscales and items
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• CCI	

3.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary clinical question of interest is: What is the effect of JDQ443 monotherapy in inducing radiological response per RECIST 1.1 assessed by BIRC when administered as first-

line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1% (cohort A), regardless of study treatment discontinuation and any unforeseen events resulting from a public health emergency?

The justification for the primary estimand is that it will capture the treatment effect irrespective of study treatment discontinuation but avoids the confounding effect of any new anti-cancer therapy that is not a part of the originally assigned treatment.

The primary estimand is described by the following attributes:

1. Population: Adult participants with locally advanced or metastatic NSCLC without previous systemic treatment for metastatic disease whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1%, irrespective of STK11 mutation status (cohort A).
2. Primary variable: BOR defined as the best response recorded from the start of the treatment until disease progression per RECIST 1.1 by BIRC, with responses documented after the use of any new anti-neoplastic therapy considered as non-response.
3. Treatment of interest: All participants enrolled in this study will be treated with JDQ443 – a selective and irreversible KRAS G12C inhibitor – administered p.o. 200 mg twice a day continuously.
4. Handling of remaining intercurrent events:
   - Treatment discontinuation for any reason: Tumor assessment data collected irrespective of treatment discontinuation will be included to derive BOR (treatment policy strategy).
   - Any public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster: tumor assessment data collected irrespective of such unforeseen events will be considered for the BOR (treatment policy strategy).
   - New anti-cancer therapy: If any new anti-neoplastic therapy is initiated, responses documented after the use of new anti-neoplastic therapy will be considered as non-response (composite strategy).
5. Summary measure: ORR defined as the proportion of participants with a confirmed CR/PR as BOR, with its corresponding two-sided exact binomial 95% confidence interval.

3.2 Secondary estimands

One secondary clinical question of interest is: What is the effect of JDQ443 monotherapy in inducing radiological response per RECIST 1.1 assessed by BIRC when administered as first-line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1% and an STK11 co-mutation (cohort B), regardless of study treatment discontinuation and any unforeseen events resulting from a public health emergency?

The justification for the secondary estimand is that it will capture the treatment effect irrespective of study treatment discontinuation but avoids the confounding effect of any new anti-cancer therapy that is not a part of the originally assigned treatment.

This secondary estimand is described by the following attributes:

1. Population: Adult participants with locally advanced or metastatic NSCLC without previous systemic treatment for metastatic disease whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1%, and an STK11 co-mutation (cohort B).
2. Primary variable: BOR defined as the best response recorded from the start of the treatment until disease progression per RECIST 1.1 by BIRC, with responses documented after the use of any new anti-neoplastic therapy considered as non-response.
3. Treatment of interest: All participants enrolled in this study will be treated with JDQ443 – a selective and irreversible KRAS G12C inhibitor – administered p.o. 200 mg twice a day continuously.
4. Handling of remaining intercurrent events:
   - Treatment discontinuation for any reason: Tumor assessment data collected irrespective of treatment discontinuation will be included to derive BOR (treatment policy strategy).
   - Any public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster: tumor assessment data collected irrespective of such unforeseen events will be considered for the BOR (treatment policy strategy)
   - New anti-cancer therapy: If any new anti-neoplastic therapy is initiated, responses documented after the use of new anti-neoplastic therapy will be considered as non-response (composite strategy).
5. Summary measure: ORR defined as the proportion of participants with a confirmed CR/PR as BOR, with its corresponding two-sided exact binomial 95% confidence interval.

A further secondary clinical question of interest is: In participants who respond to the JDQ443 monotherapy based on RECIST 1.1 assessed by BIRC, how long does the response to first-line treatment for participants in cohort A or in cohort B last, regardless of study treatment discontinuation and any unforeseen events resulting from a public health emergency?

The justification for this secondary estimand is that it will capture the duration of the treatment effect irrespective of study treatment discontinuation but avoids the confounding effect of any new anti-cancer therapy that is not a part of the originally assigned treatment.

This secondary estimand will be evaluated for both cohorts and is described by the following attributes:

1. Population:
   - Cohort A: Adult participants with locally advanced or metastatic NSCLC without previous systemic treatment for metastatic disease whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1%, irrespective of STK11 mutation status.
   - Cohort B: Adult participants with locally advanced or metastatic NSCLC without previous systemic treatment for metastatic disease whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1%, and an STK11 co-mutation.
2. Primary variable: DOR defined as time from the date of first documented response of CR or PR to the date of the first documented progression or death due to any cause, according to RECIST 1.1 assessed by BIRC for participants whose best overall response is CR or PR.

3. Treatment of interest: All participants enrolled in this study will be treated with JDQ443 – a selective and irreversible KRAS G12C inhibitor – administered p.o. 200 mg twice a day continuously.
4. Handling of remaining intercurrent events:
   - Treatment discontinuation for any reason: Tumor assessment data collected irrespective of treatment discontinuation will be included to derive DOR (treatment policy strategy).
   - Any public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster: tumor assessment data collected irrespective of such unforeseen events will be considered for the DOR (treatment policy strategy)
   - New anti-cancer therapy: If any new anti-neoplastic therapy is initiated, progression or death occurring after the use of new anti-neoplastic therapy will not be considered and the DOR censored.
5. Summary measure: Median duration of response estimated by the Kaplan-Meier method (for cohort A and B, resp.).

4 Study design

4.1 Overall design

This is a non-randomized, open-label, single-arm, multicenter, phase II study evaluating the antitumor activity and safety of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic KRAS G12C-mutated NSCLC (Figure 1-1).

The study will have 2 non-comparative cohorts that will enroll approximately 120 participants in parallel according to the following characteristics:

- **Cohort A:** participants whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1%, regardless of STK11 mutation status (N=90).
- **Cohort B:** participants whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1% and an STK11 co-mutation (N=30).

The sample size of cohorts A and B was determined based on the estimated frequency of the molecular profile required to meet eligibility criteria for each cohort: the prevalence of PD-L1 expression <1% is estimated as around 40% in patients with KRAS G12C- mutated NSCLC, whereas STK11 co-mutations are found in around 12-15% of these patients (Skoulidis et al 2015, Skoulidis and Heymach 2019, Aredo et al 2019, Ricciuti et al 2021 and Skoulidis et al 2021). Due to the differences in terms of sample size, the antitumor activity of JDQ443 will be assessed as primary objective in cohort A, and as a key secondary objective in cohort B.

The statistical analyses will be performed separately for each of the two cohorts. For both cohort A and cohort B, an interim analysis is planned to stop early for lack of efficacy (futility). The interim analysis in cohort A will be performed based on ORR in approximately the first 30 participants enrolled who have been followed for at least two tumor assessments or have discontinued the study earlier. In cohort B, the interim analysis will be based on approximately

the first 15 participants enrolled who have been followed for at least two tumor assessments or discontinued the study earlier.

Details are described in Section 9.8.

JDQ443 treatment may be continued beyond initial disease progression as per RECIST 1.1 by BIRC if, in the judgement of the Investigator, there is evidence of clinical benefit, and the participant wishes to continue on the study treatment (for additional details please refer to Section 6.1.4.1).

4.2 Scientific rationale for study design

The rationale for the study design is described below in Table 4-1.

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Participant population	KRAS G12C mutations are found in around 13% of NSCLC patients and are associated with treatment resistance, as well as with a poor prognosis (Guibert et al 2016, Del Re et al 2017, Goulding et al 2020). Although KRAS G12C inhibitors have demonstrated antitumor activity in previously treated patients with advanced NSCLC, their efficacy in the first-line setting remains unknown (Skoulidis et al 2021, Riely et 2021). Hence, the current standard first-line treatment for patients with advanced NSCLC whose tumors harbor a KRAS G12C mutation is the same as for patients whose tumors have no targetable mutations, consisting of an immune checkpoint inhibitor alone or in combination with platinum-based chemotherapy in most cases. (Planchard et al 2018, Hanna et al 2020). Patients whose tumors have a PD-L1 expression < 1% or an STK11 mutation derive less benefit from immunotherapy-based treatment, hence alternative treatments for these individuals are needed. In this phase II study, the antitumor activity and safety of the KRAS G12C inhibitor JDQ443 administered as single-agent in the first-line setting will be evaluated in 2 subgroups of participants with advanced NSCLC in whom a low benefit of immunotherapy is expected: participants whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1% (cohort A) and those whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1% and an STK11 co-mutation (cohort B).
Open-label	Considering the available evidence showing that patients with a PD-L1 expression < 1% or with an STK11 mutation derive less benefit from immunotherapy-based treatment, as well as the encouraging activity observed with KRAS G12C inhibitors in patients with advanced NSCLC, the non-randomized design(open-label) is appropriate for this study (Xu et al 2019, Ricciuti et al 2021).
Treatment beyond disease progression	After the discontinuation of targeted therapies, accelerated tumor progression and tumor lesion growth can occur in some patients, hence those patients who are deriving clinical benefit from JDQ443 treatment according to Investigator's judgment will be allowed to continue study treatment beyond initial RECIST 1.1 progression by BIRC (Chaft et al 2011).
Interim analyses	Interim analyses for futility were implemented in this study to allow an early assessment of the antitumor activity of JDQ443, as well as to allow discontinuation of the respective cohort in case futility criteria are met.

4.3 Justification for dose

The recommended Phase II dose of JDQ443 is 200 mg twice a day (b.i.d.). This was determined based on the clinical assessment of safety, PK, PK-PD modeling as well as the Bayesian hierarchical logistic regression model (BHLRM) assessing the probability of dose limiting toxicities (DLTs) from the dose escalation phase of FIH CJDQ443A12101 study, a phase Ib/II open-label, multi-center dose escalation study of JDQ443 in patients with advanced solid tumors harboring the KRAS G12C mutation. Four dose levels of JDQ443 tablets (CCI mg QD., CCI mg QD., CCI mg b.i.d. and CCI mg b.i.d.) were investigated in the dose escalation phase.

The CCI mg b.i.d. dose was evaluated and determined to be safe and tolerable. The highest AUC0-24h was obtained at CCI mg b.i.d. among all dose levels tested, >CCI% higher than the exposure for CCI mg and CCI mg QD dose levels, and was at least CCI-fold above the efficacious exposure required for maximum efficacy in less sensitive xenograft models which had the highest exposure requirement for tumor regression. At this dose level, a >CCI% average KRAS G12C target occupancy was predicted based on PK-PD modeling and was higher than the CCI% average target occupancy required for tumor regression in various xenograft models.

The CCI mg b.i.d. dose level satisfied the escalation with overdose control (EWOC) criteria (i.e. <CCI% chance that the true DLT rate was greater than or equal to CCI% during DLT evaluation period) by Bayesian hierarchical logistic regression model (BHLRM) with posterior probability of excessive toxicity less than CCI%. No DLTs were observed at this dose level. For detailed information on clinical experience of JDQ443 including safety assessments, please refer to Section 2.2.4.2.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable

4.5 Rationale for public health emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic, or natural disaster, mitigation procedures to ensure participants' safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

4.6 Purpose and timing of interim analyses/design adaptations

One interim futility analysis per cohort is planned to assess ORR independently in each cohort when approximately 30 and 15 participants, in cohort A and cohort B, respectively, have been enrolled and followed for 2 tumor assessments or have discontinued the study earlier, with the objective to allow an early assessment of the antitumor activity of JDQ443, as well as to allow the discontinuation of the respective cohort in case the futility criteria are met. For further details please refer to Section 9.8.

4.7 End of study definition

Study completion is defined as the earliest occurrence of one of the following:

- The last participant completes last study visit (and the assessments associated with this visit have been documented and followed-up appropriately by the Investigator), dies, withdraws consent or is lost to follow-up, whichever comes first.
- In the event of an early study termination decision, the date of that decision.
- Another clinical study becomes available that can continue to provide JDQ443 to study participants and all participants with ongoing treatment are transferred to that clinical study.

See Section 6.6 for information on continued access to study treatment after the end of the study.

5 Study population

The study population will include adult participants with locally advanced or metastatic squamous or non-squamous NSCLC whose tumors harbor a KRAS G12C mutation and a PD-L1 expression <1% (cohort A) or a PD-L1 expression ≥ 1% and an STK11 co-mutation (cohort B), who have not received any prior systemic treatment for metastatic disease.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Participant is an adult ≥ 18 years of age at the time of informed consent.
3. Histologically confirmed locally advanced (stage IIIb/IIIc not eligible for definitive chemoradiation or surgical resection with curative intent) or metastatic (stage IV) NSCLC.
4. Presence of a KRAS G12C mutation (all participants) and:
   - For cohort A: PD-L1 expression <1%, regardless of STK11 mutation status.
   - For cohort B: PD-L1 expression ≥ 1% and an STK11 co-mutation.

   KRAS G12C and/or STK11 mutation status assessed in tumor tissue or blood as determined by a local test, validated according to local regulation at a Clinical Laboratory Improvement Amendments CLIA-certified USA laboratory or an accredited local laboratory outside of the USA or centrally assessed at a Novartis-designated laboratory prior to enrollment.

   PD-L1 tumor proportion score (TPS) status assessed determined by local assessment at a CLIA-certified USA laboratory or an accredited local laboratory outside of the USA or centrally assessed at a Novartis designated laboratory prior to enrollment.

   For participants in China only: PD-L1 expression, KRAS G12C status and STK11 mutation status (cohort B only) must be determined by local assessment, according to criteria listed above.
5. No previous systemic treatment for metastatic disease. Prior (neo)adjuvant treatment with chemotherapy and/or immunotherapy, or prior radiotherapy administered sequentially or concomitantly with chemotherapy and/or immunotherapy for localized or locally

advanced disease are accepted if the time between therapy completion and enrollment is > 12 months.

6. ECOG performance status ≤ 1.
7. At least 1 measurable lesion by RECIST 1.1.
8. Participant must have recovered from all toxicities related to prior treatments to grade ≤ 1 (CTCAE v 5.0). Exception to this criterion are alopecia and vitiligo of any grades.
9. Adequate organ function including the following laboratory values at the screening visit:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (without growth factor support),
   - Platelets ≥ 100 x 10^9/L (without growth factor support),
   - Hemoglobin (Hgb) > 9 g/dL (7 days without transfusions or growth factor support),
   - Aspartate transaminase (AST) ≤ 3 x upper limit of normal (ULN),
   - Alanine transaminase (ALT) ≤ 3 x ULN,
   - Total bilirubin ≤ 1.5 ULN,
   - Serum amylase ≤ 2 x ULN,
   - Serum lipase ≤ 1.5 x ULN,
   - Creatinine clearance ≥ 45 mL/min by calculation using Cockcroft-Gault formula.
10. Participant is capable of swallowing study medication and following instructions regarding study treatment administration, or have a daily caregiver(s) who will be responsible for administering study treatment.
11. Participant must be able to communicate with the Investigator and comply with the requirements of the study procedures.

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are **not** eligible for inclusion in this study.

1. Participants who previously received a KRAS G12C inhibitor or any other systemic therapy for metastatic NSCLC.
   - Prior (neo)adjuvant treatment with chemotherapy or immunotherapy, or prior radiotherapy administered sequentially or concomitantly with chemotherapy and/or immunotherapy for localized or locally advanced disease are not allowed if the time between therapy completion and enrollment is ≤ 12 months.
2. Participants whose tumors harbor an EGFR-sensitizing mutation and/or ALK rearrangement by local laboratory testing. Participants with NSCLC of pure squamous cell histology are eligible if EGFR-sensitizing mutation or ALK status is unknown; however, if the presence of an EGFR-sensitizing mutation or ALK rearrangement is known, participants will be excluded.
   - Note: Participants with other known druggable alterations will be excluded, if required by local guidelines
3. History of severe hypersensitivity reaction to JDQ443 or its excipients.
4. Known active (unstable/symptomatic) central nervous system (CNS) metastases and/or carcinomatous meningitis.

- Participants with previously treated, and at the time of screening, stable brain metastases may participate provided they meet all of the following criteria:
- Brain imaging at screening shows no evidence of interim progression since previous imaging. Patients with brain metastasis found on screening are eligible to the study if asymptomatic
  - Subjects clinically stable for ≥2 weeks.
  - Have measurable and/or evaluable disease outside CNS
  - corticosteroids are allowed as therapy for CNS disease at a dose of 10 mgs prednisolone (or equivalent) or less
  - No stereotactic radiation or whole-brain radiation ≤14 days before randomization.
  - Recovered from brain metastasis surgery
  - Stable brain metastasis by this definition should be established prior to the first dose of study medication

5. Presence or history of a malignant disease, other than the resected NSCLC, that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this criterion are completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma *in situ* of any type.
6. Participant has had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to starting study treatment or has not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and the participant can be enrolled in the study ≥ 1 week after the procedure.
7. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or participants who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment is allowed.
8. Clinically significant, uncontrolled cardiac disease and/or recent cardiac events (within 6 months), such as:
   - Unstable angina or myocardial infarction within 6 months prior to screening.
   - Symptomatic congestive heart failure (defined as New York Heart Association Grade II or greater).
   - Documented cardiomyopathy.
   - Clinically significant cardiac arrhythmias.
   - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, unless controlled prior to first dose of study treatment.
9. History or current diagnosis of ECG abnormalities indicating significant risk of safety for study participation such as:

- Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker.
- History of familial long QT syndrome or known family history of Torsades de Pointes.
- Resting QT interval corrected with Fridericia's formula (QTcF) > 480 msec on screening ECG or congenital long QT syndrome

10. A medical condition that results in increased [redacted]
11. History of interstitial lung disease or pneumonitis grade ≥ 2.
12. Current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (i.e., uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes etc.).
13. Any other concurrent severe and/or uncontrolled medical condition that would, in the Investigator's judgment cause unacceptable safety risks, contra-indicate participation in the clinical study or compromise compliance with the protocol (e.g., chronic pancreatitis, uncontrolled diabetes, hepatic disorders including cirrhosis).
14. Any other medical condition (such as active infection, treated or untreated), which in the opinion of the Investigator represents an unacceptable risk for participation in the study.
    - Note: testing for hepatitis B virus (HBV) or hepatitis C virus infection, tuberculosis and/or HIV (by local laboratory) is not mandatory at screening unless if required by local regulations.
15. Any medical condition or prior surgical resection that may affect the absorption of the investigational drug. Examples of medical conditions that may affect investigational drug absorption include (but are not limited to) inflammatory bowel disease (i.e., ulcerative colitis, Crohn's disease) and gastrointestinal disease such as ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, and malabsorption syndrome.
16. Participants who are taking a prohibited medication (strong CYP3A inducers) that cannot be discontinued at least seven days prior to the first dose of study treatment and for the duration of the study (see Section 6.8.2).
17. Use of any live vaccines against infectious diseases within four weeks before initiation of study treatment.
18. Participant is concurrently using other anti-cancer therapy.
19. Participation in any additional, parallel, investigational drug or device studies.
20. Pregnant or breast-feeding women or women who plan to become pregnant or breast-feed during the study. Pregnant women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 7 days after the last dose of JDQ443. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female bilateral tubal ligation, female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or total hysterectomy at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
- In case of use of oral contraception women should have been stabilized on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks 6 weeks prior to enrollment on study. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered to be not of child-bearing potential.

22. Sexually active males unless they use a condom during intercourse while taking study treatment and for 7 days after the last dose of JDQ443. Male participants should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the study treatment via seminal fluid. In addition, male participants must not donate sperm and women participants must not donate oocytes for the time period specified above.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

5.3 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Participants who signed an informed consent form (i.e., pre-screening molecular ICF and/or Main ICF) and are subsequently found to be ineligible will be considered as screen failures.

The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, inclusion/exclusion, information on prior local testing on tumor and blood for KRAS G12C, STK11, EGFR and ALK rearrangement/mutation status, other known druggable alteration information (if available) and PD-L1 expression status, tumor sample collection (archival or newly obtained) for central confirmation of KRAS G12C and STK11 mutation and PD-L1 expression status and future *in vitro* diagnostic development, blood sample for future *in vitro* diagnostic development, NSCLC diagnosis and extent of disease, screening period disposition, withdrawal of consent/opposition to use of data/biological samples if applicable and death if applicable pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening period (see Section 8.7.3 for reporting details). For molecular pre-screening failures, only SAEs possibly related to a study procedure will be reported. Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who sign the main ICF and are considered eligible (enrolled) but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition eCRF.

IRT should be notified within 2 days if the participant did not start treatment or is not enrolled.

A new ICF will need to be signed if the Investigator chooses to re-screen the participant after a participant has screen failed. All re-screening evaluations must be performed within 28 days prior to start of study treatment. All required screening activities must be performed when the participant is rescreened for participation in the study. If the participant completes all re-screening evaluations and still does not meet the eligibility criteria, the participant is a screen failure and cannot be re-screened again (only one re-screening allowed). Once the number of participants screened and enrolled is likely to reach the target enrollment, the Sponsor may close the study to further screening. In this case, the participants who screen failed will not be permitted to be re-screened.

5.3.1 Participant numbering

Participant numbering can be configured as a four-digit site number followed by a consecutive three-digit number, e.g., 1234001, 1234002 where the site number is 1234.

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is rescreened. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the Investigator chooses to rescreen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

For this study, the term "study treatment" refers to Novartis study drug JDQ443, which will be labeled and provided to sites by Novartis in compliance with legal requirements for each country. The study treatment begins on Cycle 1 Day 1 (C1D1) with the first administration of JDQ443.

All doses prescribed, dispensed to the participant and all dose changes during the study, including the reason, must be recorded on the appropriate electronic case report form (eCRF) page.

Table 6-1 Investigational drug

Treatment Title	JDQ443
Treatment Description	Tablets given as 200 mg b.i.d. with food
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	100 mg
Dosage Level(s)	200 mg b.i.d.
Route of Administration	Oral
Use	Experimental
IMP (Investigational medicinal product)	Yes
Sourcing	Provided centrally by the sponsor
Packaging and Labelling	Study treatment will be provided in HDPE bottles. Each bottle will be labelled as required per country requirement.

6.1.1 Additional study treatments

No other study treatment beyond JDQ443 is included in this trial.

6.1.2 Treatment arms/group

The study will have 2 non-comparative cohorts that will recruit participants in parallel according to the following characteristics:

- **Cohort A**: participants whose tumors harbor a KRAS G12C mutation and a PD-L1 expression <1%, regardless of STK11 mutation status.
- **Cohort B**: participants whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1% and an STK11 co-mutation.

Participants will be assigned at enrollment to one of the cohorts. Participants in both cohorts will receive JDQ443 200 mg b.i.d. administered continuously with food. The day of the first tablet taken defines C1D1. Each treatment cycle is 21 days for both arms.

6.1.3 Guidelines for continuation of treatment

Participants should continue to receive the study treatment until one or more criteria for treatment discontinuation described in Section 7 are met.

Guidelines on the management of common JDQ443 associated toxicities and dose modification instructions are provided in Section 6.5.

6.1.4 Treatment duration

Participants will be treated until they experience any of the following: unacceptable toxicity, disease progression per RECIST 1.1 by BIRC and/or treatment is discontinued at the discretion of the Investigator or the participant. A complete list of the circumstances requiring study treatment discontinuation is provided in Section 7.1

While the Investigator is waiting for the results from the central imaging vendor to confirm disease progression, the participant should continue on study treatment. However, during this time, the Investigator should do whatever is medically necessary and indicated for the participant.

Participants treated with JDQ443 may continue treatment beyond disease progression per RECIST 1.1 by BIRC if in the judgment of the Investigator there is evidence of clinical benefit and the participant wishes to continue on the study treatment. Criteria for treatment beyond progression are described in Section 6.1.4.1 .

See Section 6.6 for information on continued access to study treatment after the end of the study.

6.1.4.1 Treatment beyond disease progression

Participants treated with JDQ443 will be permitted to continue study treatment beyond initial disease progression per RECIST 1.1 by BIRC, provided they meet all the following criteria:

- Evidence of clinical benefit assessed by Investigator
- No rapid disease progression
- Adequate tolerance to study treatment as defined by no grade 3 or 4 toxicities within the past 21 days on current therapy
- Should not jeopardize critical interventions to treat/prevent severe complications, or prevent participants from receiving adequate care
- Participant performance status is stable
- Participant wishes to continue on the study treatment
- No new antineoplastic therapy has been initiated

Treatment beyond disease progression should not jeopardize critical interventions to treat/prevent severe complications or prevent participants from receiving adequate care.

The reasons for the participant continuing treatment beyond progression will be documented in the eCRF.

Participants who meet the above criteria and continue treatment beyond initial disease progression will continue all study procedures as outlined in the visit scheduled assessments. Clinical deterioration or suspicion of further disease progression will require a follow-up imaging assessment to be performed promptly rather than waiting for the next scheduled assessment. Participants who are no longer deriving clinical benefit, or who meet other protocol discontinuation criteria must be discontinued from study treatment.

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Section 6.1.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 3 cycles supply. In this case, regular phone calls or virtual contacts (every 3 weeks minimum, or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the JDQ443 bottle label.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator or designated site staff must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local

regulation/guidelines. Otherwise, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.2.2 Handling of other treatment

Not Applicable

6.2.3 Instruction for prescribing and taking study treatment

All dosages prescribed and dispensed to participants and all dose changes during the study must be recorded on the Dose Administration Record eCRF. Doses and treatment schedules are described in Table 6-2.

Table 6-2 Dose and treatment schedule

Investigational Drug (Name and Strength)	Dose	Frequency and/or Regimen
JDQ443 (100 mg)	200 mg (2 x 100 mg)	Twice a day (b.i.d)

JDQ443 will be administered orally as a flat-fixed dose.

A sufficient supply of JDQ443 should be provided to participants to allow study treatment self-administration at home until at least the next study visit at the clinic. At subsequent visits, site staff will provide additional bottles to ensure the study treatment supply until discontinuation of study treatment.

Participants should take their dose at approximately the same time each day. The first daily dose should be taken in the morning and the second dose should be taken approximately 12 h after the first dose (e.g., 08:00 and 20:00). If a dose is not taken within 4 h of the planned dosing time, the missed dose should not be replaced

JDQ443 should be administered with food. Participants should take JDQ443 immediately (within 30 minutes) following a meal.

Each dose of JDQ443 is to be taken with a glass of water and consumed over as short time as possible.

The tablets should be ingested whole and should not be chewed or crushed.

If vomiting occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose. If the vomiting occurs on PK sampling days within the first 4 h post-dosing, this event should be recorded on the dose administration PK electronic eCRF page, as well as on the AE eCRF, as appropriate.

On days when PK blood samples are to be collected, participants will be instructed to hold their dose until arrival at the study center. JDQ443 will be administered with food at the site in the morning prior to the PK blood draws, except for pre-dose samples which will be collected immediately before JDQ443 administration. The administration will be supervised by a member of the research team. The dose, exact date and time of drug administration, exact date and time of PK blood draws, and meal record (start/end time) should be recorded in the appropriate eCRF.

The Investigator or responsible site personnel should instruct the participant to take the study treatment exactly as prescribed to promote compliance.

Participants should inform the investigational site staff of any missed or delayed doses.

CCI [redacted]

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

No randomization will be performed in this study. The assignment of a participant to a particular cohort will be driven by eligibility criteria and coordinated by Novartis. The response assessment for the study's primary endpoint according to RECST 1.1 will be performed by BIRC in order to mitigate the risk of bias.

6.3.2 Treatment blinding

Not Applicable

6.3.3 Emergency breaking of assigned treatment code

Not Applicable

6.4 Study treatment compliance

The date and time of study treatment administration during the study and any deviations from the protocol treatment schedule will be captured on the appropriate study treatment dispensation form.

The Investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant’s safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed.

For JDQ443, compliance will be assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.5 Dose modification

6.5.1 Dose modification guidelines

For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions are either recommended or mandated in order to allow participants to continue the study treatment.

These dose modifications for JDQ443 are summarized in Table 6-3 and Table 6-4. Deviations to mandatory dose interruptions and/or reductions are not allowed. Permanent discontinuation from study treatment is mandatory for specific events indicated as such in Table 6-3 and Table 6-4.

Dose reductions are allowed for JDQ443 and should follow the dose reduction steps described in Table 6-3 and Table 6-4. For each participant, a maximum of two consecutive dose level reductions is allowed after which the participant must be discontinued. Dose reductions of JDQ443 below 100 mg QD. are not permitted.

Dose re/escalation of JDQ443 to previous dose level is allowed only once, and if no AE leading to dose modification is observed after at least 1 cycle (21 days) of study treatment at the reduced dose.

For toxicities related to study treatment that resolve within 7 days of event onset, treatment may be resumed at the same or a lower dose level at the Investigator's discretion, except for toxicities that require permanent treatment discontinuation (Table 6-3 and Table 6-4).

For toxicities related to study treatment that result in dose interruptions of more than 7 but not more than 21 days, study treatment may be resumed but only at a lower dose level. If the participant is already at the lowest dose level, participant might continue receiving treatment at the same dose level if participant is deriving clinical benefit from JDQ443. In such situation, the Investigator must discuss and receive approval from Novartis Medical Monitor or designee prior to continuing JDQ443 and rationale should be captured in the source document.

If the participant requires a dose interruption of more than 21 days from the intended day of the next scheduled dose, then the participant must be discontinued from the study treatment. Exceptions to this criterion may be considered if the participant is deriving clinical benefit from the treatment. The Investigator must discuss and receive approval from Novartis Global Medical Director or designee prior to continuing study treatment in this situation and rationale should be captured in the source documents. If study treatment is reintroduced after an interruption of more than 21 days caused by an adverse event, study treatment can only be reintroduced at a lower dose level. If study treatment is reintroduced after an interruption of more than 21 days that was not caused by an adverse event, study treatment may be reintroduced without dose reduction.

All dose changes must be recorded on the appropriate eCRF.

Table 6-3 Criteria for dose reduction / interruption and re-initiation of JDQ443 treatment for adverse drug reactions.

Dose modifications for JDQ443	
Worst toxicity CTCAE Grade[a] (value) during a cycle of therapy	
Investigations (Hematologic)	
Neutropenia (ANC)	
Grade 1 (ANC < lower limit of normal (LLN) - 1500/mm^3)	Recommendation: Maintain study treatment and dose level.
Grade 2 (ANC < 1500 - 1000/mm^3)	Recommendation: Maintain study treatment and dose level.
Grade 3 (ANC < 1000 - 500/mm^3)	Recommendation: Interrupt study treatment until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, maintain dose level. If resolved in > 7 days, reduce 1 dose level.
Grade 4 (ANC < 500/mm^3)	Mandatory: Interrupt study treatment until resolved to ≤ Grade 2, then reduce 1 dose level.
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Recommendation: Maintain study treatment and dose level.
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Recommendation: Maintain study treatment and dose level.
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Recommendation: Interrupt study treatment until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, maintain dose level. If resolved in > 7 days, reduce 1 dose level. Mandatory: For Grade 3 thrombocytopenia associated with major bleeding, permanently discontinue study treatment.
Grade 4 (PLT < 25,000/mm^3)	Mandatory: Interrupt study treatment until resolved to ≤ Grade 2, then reduce 1 dose level. Mandatory: For Grade 4 thrombocytopenia associated with major bleeding, permanently discontinue study treatment.
Febrile neutropenia (ANC < 1.0 × 10^9/L, with a single temperature of >38.3 degrees C [101 degrees F] or a sustained temperature of ≥ 38 degrees C [100.4 degrees F] for more than one hour)	Mandatory: Interrupt study treatment until resolved, then reduce 1 dose level.
Anaemia	
Grade 1 (Hemoglobin [Hgb] < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Recommendation: Maintain study treatment and dose level.
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 – 4.9 mmol/L; < 100 - 80 g/L)	Recommendation: Maintain study treatment and dose level.
Grade 3 (Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated)	Recommendation: Interrupt study treatment until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume study treatment at the same dose level; If resolved in > 7 days, reduce 1 dose level.
Grade 4 (Life-threatening consequences; urgent intervention indicated)	Mandatory: Interrupt study treatment until resolved to ≤ grade 2, then reduce 1 dose level.

Investigations (Renal)	
Serum creatinine	
Grade 1 (> ULN - 1.5 × ULN)	Recommendation: Maintain study treatment and dose level.
Grade 2 (> 1.5 - 3.0 × ULN)	Recommendation: Interrupt study treatment and manage according to institutional practice. Upon resolution to ≤ Grade 1, may reintroduce study treatment at the same dose level if clinically indicated.
Grade 3 (> 3.0 - 6.0 × ULN) and Grade 4 (> 6.0 × ULN)	Mandatory: Permanently discontinue study treatment.
Investigations (Hepatic)	
Isolated total Bilirubin elevation	
Grade 1 (> ULN – 1.5 × ULN)	Recommendation: Maintain study treatment and dose level.
Grade 2 (> 1.5 - 3.0 × ULN)	Recommendation: Interrupt study treatment. Repeat LFTs[b] within 48-72 hours, then monitor LFTs at least weekly, until resolved to ≤ 1.5 × ULN or to baseline, then: • If resolved in ≤ 7 days, resume study treatment at the same dose level; • If resolved in > 7 days, reduce 1 dose level.
Grade 3 (> 3.0 - 10.0 × ULN)*	Recommendation: Interrupt study treatment. Repeat LFTs[b] within 48-72 hours, then monitor LFTs at least weekly, until resolved to ≤ 1.5 × ULN or to baseline. May reintroduce study treatment at 1 lower dose level if clinically indicated.
Grade 4 (> 10.0 × ULN)*	Mandatory: Permanently discontinue study treatment. The participant should be monitored at least weekly (including LFTs[b]), or as clinically indicated, until total bilirubin has resolved to ≤ 1.5 × ULN or to baseline. Note: An isolated bilirubin elevation is not typical for treatment-induced liver injury. Bilirubin can be elevated either as part of a “Hy’s law” constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin elevation can be seen in conjunction with treatments that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation should be excluded before basing dose modification decisions on bilirubin values alone.
Isolated AST or ALT elevation	
If normal at baseline:	
Grade 1 (> ULN - ≤ 3.0 × ULN)	Recommendation: Maintain study treatment and dose level.
Grade 2 (> 3.0 - ≤ 5.0 x ULN)	Recommendation: Interrupt study treatment. Repeat LFTs[b] within 48-72 hours, then monitor LFTs at least weekly, until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, resume study treatment at the same dose level;

	• If resolved in > 7 days, reduce 1 dose level.
Grade 3 (> 5.0 - ≤ 20.0 x ULN)	Recommendation: Interrupt study treatment. Repeat LFTs[b] within 48-72 hours, then monitor LFTs at least weekly, until resolved to ≤ Grade 1, then reduce 1 dose level.
Grade 4 (> 20.0 x ULN)	Mandatory: Permanently discontinue study treatment. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] at least weekly, until resolved to grade ≤1or stabilization over 4 weeks.
If elevated at baseline (up to Grade 1: ≤ 3.0 x ULN):	
> 5.0 x ULN AND ≤ 3.0 x baseline	Recommendation: Interrupt study treatment. Repeat LFTs[b] within 48-72 hours, then monitor LFTs at least weekly, until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, resume study treatment at the same dose level; • If resolved in > 7 days, reduce 1 dose level.
>10 x ULN AND > 3.0 x baseline	Recommendation: Interrupt study treatment. Repeat LFTs[b] within 48-72 hours, then monitor LFTs at least weekly, until resolved to ≤ Grade 1, then reduce 1 dose level.
> 20.0 x ULN	Mandatory: Permanently discontinue study treatment. Repeat LFTs[b] as soon as possible, preferably within 48-72 hours from awareness of the abnormal results; monitor LFTs[b] at least weekly, until resolved to baseline or stabilization over 4 weeks.
Combined[c] elevations of AST or ALT and total bilirubin	
For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT >3.0 × ULN combined with total bilirubin > 2.0 × ULN without evidence of cholestasis[d] and Gilbert's syndrome **For participants with elevated baseline AST or ALT or total bilirubin value:** AST or ALT > 3 × baseline OR > 8.0 × ULN, whichever is lower, combined with total bilirubin > 2 × baseline AND > 2.0 × ULN Note: For participants with Gilbert's syndrome, at least 2-fold increase in direct bilirubin.	Mandatory: Interrupt study treatment and adjudicate for DILI: Repeat as soon as possible, preferably within 48 hours from awareness of the abnormal results, monitor LFTs[b] at least weekly, or as clinically indicated, until AST, ALT, and total bilirubin have resolved ≤ Grade 1 or to baseline. If causality assessment indicates that DILI is confirmed: Permanently discontinue study treatment. If not DILI: Treat the identified cause according to institutional guidelines. Once resolved to ≤ Grade 1 or to baseline, may reintroduce study treatment at 1 lower dose level if clinically indicated, following discussion with Novartis medical monitor. Refer to Section 6.5.3.1 for further details on the follow up of potential drug-induced liver injury (DILI) cases.
Investigation (metabolic)	
amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 × ULN)	Recommendation: Maintain study treatment and dose level.
Grade 2 (> 1.5 - 2.0 × ULN)	Recommendation: Maintain study treatment and dose level.

Grade 3 (> 2.0 - 5.0 × ULN) with signs or symptoms; > 5.0 × ULN and asymptomatic.**	Recommendation: Interrupt study treatment until resolved to Grade ≤ 1 or baseline, then: If resolved in ≤ 7 days, resume study treatment at the same dose level. If resolved in > 7 days, reduce 1 dose level.
Grade 4 (> 5.0 × ULN with signs or symptoms)**	Mandatory: Permanently discontinue study treatment.
Cardiac Investigations	
Left Ventricular Ejection Fraction (LVEF)	
LVEF < 40%	Mandatory: Interrupt study treatment, obtain consultation with cardiologist and repeat cardiac imaging after 3 weeks. If improved to > 45%, restart study treatment at the same dose. If not improved to >45%, permanently discontinue study treatment.
LVEF 40%- ≤45% and decrease is ≥ 10%-points below baseline	Mandatory: Interrupt study treatment, obtain consultation with cardiologist and repeat cardiac imaging after 3 weeks. If LVEF has recovered to within 10%-point below baseline, restart study treatment at the same dose. If LVEF has not recovered to within 10%-points below baseline, permanently discontinue study treatment.
LVEF 40% to ≤45% and decrease is < 10%-points below baseline	Mandatory: Continue treatment. Obtain consultation with a cardiologist and repeat LVEF assessment within 3 weeks. If LVEF is stable/improving, no further action is needed. If there is a further decrease in LVEF, please follow the above guidance.
ECG QTc-Interval prolonged	
Grade 1 and 2	Recommendation: Maintain treatment and dose level.
Grade 3	Mandatory: Interrupt study treatment. Upon resolution to Grade ≤ 1 or baseline or < 30 msec difference from baseline (QTc), reduce 1 dose level. May resume JDQ443 treatment without dose modification after discussion with the Novartis Medical Monitor if other contributing factors have been identified. Baseline ECG refers to the ECG(s) collected at screening.
Grade 4	Mandatory: Permanently discontinue study treatment.
Vascular disorders	
Hypertension	
Grade 1 and 2	Recommendation: Maintain study treatment and dose level.
Grade 3	Recommendation: Interrupt study treatment until resolved to ≤ Grade 1, then reduce 1 dose level.
Grade 4	Mandatory: Permanently discontinue study treatment.
Gastrointestinal	
Diarrhea* **	
Grade 1	Recommendation: Maintain study treatment and dose level. Treat the patient per institutional practice.
Grade 2	Recommendation: Interrupt study treatment until resolved to ≤ grade 1, treat the patient per institutional practice, then reintroduce study treatment at the same dose level.

	If diarrhea returns as ≥ grade 2, then interrupt study treatment until resolved to ≤ grade 1 and reduce 1 dose level.
Grade 3	Recommendation: Interrupt study treatment until resolved to ≤ Grade 1, treat the patient per institutional practice, then: If resolved in ≤ 48 hours, maintain dose level. If resolved in > 48 hours despite the use of optimal anti-diarrhea therapy, reduce 1 dose level.
Grade 4	Mandatory: Permanently discontinue study treatment.
Nausea & Vomiting	
Grade 1 and 2	Recommendation: Maintain study treatment and dose level, provide anti-emetic treatment per institutional practice.
Nausea Grade 3 and Vomiting Grade ≥ 3 (despite standard anti-emetics)	Recommendation: Maintain dose level. If not resolved to ≤ Grade 2 within 48 hours after start of optimal anti-emetic therapy, interrupt study treatment until resolved to ≤ Grade 2, and resume study treatment at 1 lower 1 dose level.
Dose modifications apply to participants who experience nausea and/or vomiting despite appropriate anti-emetic treatment, which should be initiated at the first sign of nausea and/or vomiting.	
Endocrine toxicities	
Hypothyroidism or Hyperthyroidism	
Grade 1 and Grade 2	Recommendation: Maintain study treatment and dose level.
Grade 3 and Grade 4	Mandatory: Interrupt study treatment. Obtain endocrinology consultation. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification. Consideration to restart study treatment before resolution to Grade ≤ 1 with appropriate management may be considered following discussion with Novartis medical monitor.
Other endocrine disorders	
Grade 1	Recommendation: Maintain study treatment and dose level.
Grade 2 and Grade 3	Recommendation: Interrupt study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	Mandatory: Interrupt study treatment, obtain endocrinologist consultation. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment at 1 lower dose level after discussion with the Novartis Medical Monitor and consultation with an endocrinologist. Grade 4 treatment-related endocrinopathies, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require dose reduction after discussion with and approval from the Novartis Medical Monitor.

Pulmonary toxicity	
Suspected interstitial lung disease (ILD) or non-infectious pneumonitis	
Grade 1	Recommendation: Maintain study treatment and dose level. Exclude infections and other etiologies.
Grade 2	Recommendation: Interrupt study treatment during diagnostic workup for ILD/pneumonitis. Exclude infections and other etiologies. First occurrence: Upon resolution to ≤ Grade 1 in ≤ 7 days, study treatment may be reintroduced at 1 lower dose level. Monitor pulse oximetry daily for 2 weeks and perform chest x-ray 2 weeks after re-initiation, or sooner if clinically indicated. If symptoms fail to resolve within 7 days or recur after reintroduction of study treatment, permanently discontinue study treatment. Second occurrence: Permanently discontinue study treatment.
Grade 3 and Grade 4	Mandatory: Confirmed ILD Permanently discontinue study treatment.
Skeletal muscle toxicity	
Grade 1	Recommendation: Maintain study treatment and dose level.
Grade 2 and Grade 3	Recommendation: Interrupt study treatment. Consider resuming study treatment without dose modification upon resolution to ≤ Grade 1 with appropriate management.
Grade 4	Mandatory: Permanently discontinue study treatment. In some cases, reintroduction of study treatment may be considered after discussion with the Novartis Medical Monitor and consultation with a rheumatologist.
Neurological toxicity	
Any neurological adverse events	
Grade 1	Recommendation: Maintain study treatment and dose level.
Grade 2 and above	Mandatory: Interrupt study treatment until evaluation by neurologist and discussion with Novartis Medical Monitor.
Skin and subcutaneous tissue disorders	
Rash/CCI [redacted]	
Grade 1	Recommendation: Maintain study treatment and dose level and treat the participant per institutional practice. Consider initiating appropriate therapy for cutaneous toxicity (such as antihistamines, topical corticosteroids or low-dose systemic corticosteroids).
Grade 2	Recommendation: Consider interrupting study treatment and treat the participant per institutional practice initiate/intensify appropriate therapy for cutaneous toxicity (such as antihistamines, topical corticosteroids or low-dose systemic corticosteroids). If study treatment is interrupted, upon resolution to ≤

	Grade 1, resume study treatment at the same dose level.
Grade 3, despite appropriate therapy for cutaneous toxicity	Recommendation: Interrupt study treatment until resolved to Grade ≤ 1 and treat the participant per institutional practice then: If resolved in ≤ 7 days, reduce 1 dose level. If resolved in > 7 days (despite appropriate therapy for cutaneous toxicity), permanently discontinue study treatment.
Grade 4, despite appropriate therapy for cutaneous toxicity	Mandatory: Permanently discontinue study treatment.
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 and 2	Recommendation: Maintain study treatment and dose level.
Grade 3	Recommendation: Interrupt study treatment until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, maintain dose level. If resolved in > 7 days, reduce 1 dose level.
Ocular (uveitis, eye pain, blurred vision)	
Grade 1	Recommendation: Maintain study treatment and dose level. Ophthalmology consultation is required within 72 hours, except for dry eye.
Grade 2	Recommendation: Interrupt study treatment. Urgent ophthalmology consultation. Upon resolution to ≤ Grade 1 in < 14 days, may consider reintroducing study treatment without dose reduction after discussion with the Novartis medical Monitor and consultation with ophthalmology. Upon resolution to ≤ Grade 1 in ≥ 14 days, study treatment may be reintroduced at 1 lower dose level after discussion with the Novartis Medical Monitor and consultation with ophthalmology.
Grade 3 and Grade 4	Mandatory: Permanently discontinue study treatment. Urgent ophthalmology consultation.
Retinal vein occlusion or Retinal detachment	
Any Grade	Mandatory: Permanently discontinue study treatment. Urgent ophthalmology consultation.
Other adverse events	
Grade 1 and 2	Recommendation: Maintain study treatment and dose level.
Grade 3	Recommendation: Interrupt study treatment until resolved to ≤ grade 1, then reduce 1 dose level. Mandatory: Interrupt study treatment for ≥ grade 3 vomiting or grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal anti-emetic therapy (as per local practice).
Grade 4	Mandatory: Permanently discontinue study treatment.

[a] Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0)

[b] Core LFTs consist of ALT, AST, GGT, total bilirubin (fractionated [direct and indirect], if total bilirubin > 2.0 x ULN), and alkaline phosphatase (fractionated [quantification of isoforms], if alkaline phosphatase > 2.0 x ULN)

[c] "Combined" defined as total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold

If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g., permanently discontinue treatment at the situation when omit dose is needed for one parameter and permanently discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction

[d] "Cholestasis" defined as ALP elevation (> 2.0 × ULN and R value < 2) in participants without bone metastasis or elevation of ALP liver fraction in participants with bone metastasis

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R > 2 and < 5) liver injury

* Note: If total bilirubin > 3.0 × ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduce 1 dose level and continue treatment at the discretion of the Investigator.

** Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 elevation of amylase and/or lipase. If asymptomatic Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, participants will be permanently discontinued from study treatment.

*** Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools, or overt diarrhea

**** Note: JDQ443 has shown CCI . The Investigators should recommend the use of precautionary measures against CCI to the participants during treatment with JDQ443 CCI

Table 6-4 Dose reduction steps for JDQ443

Dose reduction*	Starting dose level 0	Dose level – 1	Dose level – 2
JDQ443	200 mg b.i.d.	100 mg b.i.d.	100 mg QD. (once a day)**

*Dose reduction should be based on the worst toxicity demonstrated at the last dose.

**Dose reduction below 100 mg once a day is not allowed.

6.5.2 Definitions of dose limiting toxicities (DLTs)

Not Applicable

6.5.3 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologists, endocrinologists, dermatologists, psychiatrists, neurologists etc., should be consulted as deemed necessary. All participants must be followed up for adverse events and serious adverse events for 30 days following the last doses of study treatment.

Table 6-5 outlines the follow-up evaluation recommended for toxicities of specific types and CTCAE grades.

Table 6-5 Follow-up evaluations for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
Blood and lymphatic system disorders	Test once a week until ≤ CTCAE grade 1, then restart treatment. Continue to test weekly until resolution to baseline or stabilization.
Investigations (hematologic) Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3	Test once a week until ≤ CTCAE grade 1, then restart treatment. Continue to test weekly until resolution to baseline or stabilization. Perform physical exam for check on bruising in case of major thrombocytopenia.
Investigations (metabolic) Amylase or lipase ≥ CTCAE grade 3	Test once a week until ≤ CTCAE grade 2, then restart treatment. Continue to test weekly until resolution to ≤ CTCAE grade 1 or stabilization. A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result, to exclude disease progression or potential other liver disease. In participants with serum triglycerides ≥ 500 mg/dL, urine amylase also needs to be tested.
Cardiac disorders QT and ECG ECG changes indicative of ischemic event	Twice weekly ECGs until normalization or stabilization of ECG findings then restart treatment.

6.5.3.1 Follow up on potential drug-induced liver injury (DILI) cases

Transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI. These cases should be considered as clinically important events and assessed appropriately to establish the correct diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 × ULN combined with total bilirubin > 2.0 × ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT >3.0 × baseline] OR [ALT or AST > 8.0 × ULN], whichever occurs first, combined with [total bilirubin > 2.0 × baseline AND > 2.0 × ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed to be the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, Gamma-glutamyl transferase (GGT), prothrombin time (PT)/ International Normalized Ratio (INR), alkaline phosphatase, albumin, and creatine kinase. If available, testing of Glutamate Dehydrogenase (GLDH) is additionally recommended.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – e.g. using CT, Magnetic Resonance Imaging (MRI), or duplex sonography.

Perform relevant examinations (Ultrasound or MRI, Endoscopic retrograde cholangiopancreatography (ERCP)) as appropriate, to rule out an extrahepatic cause of cholestasis. Cholestasis (is defined as an ALP elevation > 2.0 × ULN with R value < 2 in participants without bone metastasis, or elevation of the liver-specific ALP isoenzyme in participants with bone metastasis).

Note: The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R ≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury. In clinical situations where it is suspected that ALP elevations are from an extrahepatic source, the GGT can be used if available. GGT may be less specific than ALP as a marker of cholestatic injury, since GGT can also be elevated by enzyme induction or by ethanol consumption. It is more sensitive than ALP for detecting bile duct injury.

Table 6-6 provides guidance on specific clinical and diagnostic assessments which can be performed to rule out possible alternative causes of observed LFT abnormalities.

If required, these laboratory tests will be performed at the local laboratory.

Table 6-6 Guidance on specific clinical and diagnostic assessments

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	Antinuclear Antibodies (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic congestive heart failure, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 years old)	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon participants' medical history (hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; cardiovascular disease / ischemic hepatitis – ECG, prior hypotensive episodes; Type 1 diabetes mellitus / glycogenic hepatitis). If required, these laboratory tests will be performed at the local laboratory.

Obtain PK sample to determine exposure to study treatment and metabolites.

Following appropriate causality assessments, as outlined above, the causality of the treatment is estimated as "probable" (i.e., > 50% likely), if it appears greater than all other possible causes of liver injury combined. The term "treatment-induced" indicates probably caused by the treatment, not by something else, and only such a case can be considered a DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as a SAE using the term "potential treatment-induced liver injury." All events should be followed up with the outcome clearly documented.

6.6 Continued access to study treatment after the end of the study

Novartis will make every effort to supply JDQ443 to participants who may benefit from continued treatment as per the Investigator's opinion. Safety will be monitored and reported to health authorities per regulatory requirements.

6.6.1 Post-trial access

Participants who complete participation in this trial and continue to derive clinical benefit from the treatment based on the Investigator's evaluation may receive post-trial access. Post-Trial Access (PTA) means the provision of treatment to trial participants following their completion of trial participation. PTA will be provided until one of the following is met: participant no longer derives clinical benefit, Investigator discontinues treatment, launch or reimbursement (where applicable), treatment fails to achieve registration in the trial participant's country, or the clinical program is discontinued for any other reason.

Mechanisms for provision of PTA may include a rollover protocol, or provision of the Novartis investigational product in a non-trial setting (known as post-study drug supply [PSDS]), or any other mechanism appropriate for the country.

The PTA mechanism must comply with local laws and regulations in the participating trial countries. If Novartis discontinues the PTA for this trial, Novartis will work with Investigators to transition participants to locally available alternative treatments, or standard of care, where permitted and in accordance with local laws and regulations.

6.7 Treatment of overdose

In the event of an overdose, the Investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose.

Refer to [JDQ443 Investigator's Brochure] for further details related to the treatment of overdose of JDQ443.

Refer to Section 8.7 for more details on safety reporting.

6.7.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

For more information on AE and SAE definition and reporting requirements, please see Section 8.7.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded in the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator can contact the Novartis Medical Monitor before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, the investigator should contact Novartis Medical Monitor to determine if the participant should continue participation in the study.

The participant must be told to notify the investigational site about any new medications he/she takes after the start of the study treatment. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements and vitamins.

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the participant are allowed except when specifically prohibited (see Section 6.2.2).

All medications (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose administration of study treatment until 30 days after the last dose of study treatment will be recorded in the Concomitant Medications or Surgical and Medical Procedures eCRF, respectively. After starting a new antineoplastic therapy, only concomitant medications used to treat AEs or SAEs suspected to be related to study treatment should be reported.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to participants
- No anticancer agents other than the study medication should be given to participants

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

Permitted therapy to be used with caution when concomitantly used with JDQ443 include:

- Strong CYP3A inhibitors

Co-administration of JDQ443 with strong CYP3A inhibitors may increase the exposure to JDQ443. Monitor participants closely for symptoms that may be related to the increase of JDQ443 exposure.

- Sensitive substrates or substrates with narrow therapeutic index for CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A

JDQ443 is likely to inhibit these cytochrome P450 (CYP) isoforms at clinically relevant concentrations. When used concomitantly with JDQ443, monitor participants closely for symptoms of increased exposure of these substrates. Consult the product information for these substrates when considering dose adjustment.

- P-gp, OATP1B1/3 substrates

JDQ443 is likely to inhibit hepatic OATP1B1 and OATP1B3, as well as intestinal P-gp in humans. When used concomitantly with JDQ443, monitor participants closely for symptoms of increased exposure to P-gp or OATP1B1/3 substrates. Consult the concomitant P-gp or OATP1B1/3 substrate product information when considering dose adjustment.

- Herbal preparations/medications.

Refer to Section 10.7 (Appendix 7) for a list of medications that should be used with caution.

6.8.1.2 Use of bone modifying agents

Treatment with bisphosphonates or receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors for pre-existing bone metastases is permitted, if clinically indicated and at the Investigator's discretion following existing local guidelines. Treatment with bisphosphonates or RANKL inhibitors should preferably begin before the study treatment is initiated, but can also be initiated during study treatment only if absence of radiological bone disease progression is well documented (in this case, the reason for its use must be clearly documented, i.e., “pre-existing, non-progressing, bone metastases”).

6.8.1.3 Palliative radiotherapy

Local bone radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be performed if required. Radiotherapy should not be delivered to a target lesion. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and disease progression per RECIST 1.1 must be ruled out. The study treatment must be interrupted during the days of radiotherapy and can be resumed the day after its completion. The radiotherapy must be documented in the appropriate eCRF.

6.8.2 Prohibited medication

During the course of the study, participants must not receive other additional investigational drugs, devices, chemotherapy, or any other therapies that may be active against cancer.

The following medications are prohibited 7 days prior to the start of JDQ443 treatment and for the duration of the study:

- Strong CYP3A inducers

The primary biotransformation pathway for JDQ443 was CCI with some contribution from oxidative metabolism mainly via CYP3A4. Despite that oxidative metabolism via CYP3A4 being a minor pathway compared to CCI, upon induction, it may become significant and lead to a large impact on the overall clearance of JDQ443. Therefore, coadministration of strong CYP3A inducers is prohibited during treatment with JDQ443 (refer to Appendix 7, Section 10.7).

The use of live vaccines is not allowed for the duration of the study. Inactivated vaccines are allowed.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration, if any) and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian decision
- Investigator decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Section 10.7)
- Any situation in which continued study participation might result in a safety risk to the participant
- Disease progression per RECIST 1.1 by BIRC. In some circumstances, participants treated with JDQ443 may be allowed to continue to receive study treatment beyond disease progression per RECIST 1.1 by BIRC. These participants will continue assessments as outlined in Section 1.3, as applicable, and will complete the EOT visit only after permanent discontinuation of study treatment (see Section 6.1.4)
- Adverse event requiring permanent discontinuation of study treatment (see Section 6.5.1)
- Protocol deviation that results in a significant risk to participant's safety
- Withdrawal of consent (see Section 7.3)
- Study is terminated by the sponsor (see Section 7.5)
- Death
- Lost to follow-up

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in Section 1.3 Schedule of Activities.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment.

7.1.1 Follow-up for safety evaluations

All treated participants should have a safety follow-up conducted at least 30 days after the last administration of study treatment. All SAEs reported during this time period must be reported as described in Section 8.7.3

7.1.2 Follow-up for efficacy evaluations and PROs

Participants who discontinue study treatment without prior documented disease progression will continue efficacy assessments during the post-treatment efficacy follow-up, until documented disease progression per RECIST 1.1 by BIRC, participant withdrawal of consent/opposition to use of data /biological samples, investigator's decision, lost to follow-up, death or if study is terminated by the sponsor. For all participants, PRO will also continue to be collected (PRO Follow-up) until documented progression, and at a minimum of three time points following disease progression (refer to Section 8.6.1). All SAEs reported during this time period must be reported as described in Section 8.7 .

7.1.3 Overall Survival

All participants will enter the survival follow-up period once they complete the safety follow-up and efficacy follow-up after treatment discontinuation (whichever is longer). Survival status will be collected every 12 weeks (+/- 14 days) regardless of treatment discontinuation reason (except if consent is withdrawn or participant is lost to follow-up) until death, lost to follow-up, or withdrawal of consent for survival follow-up.

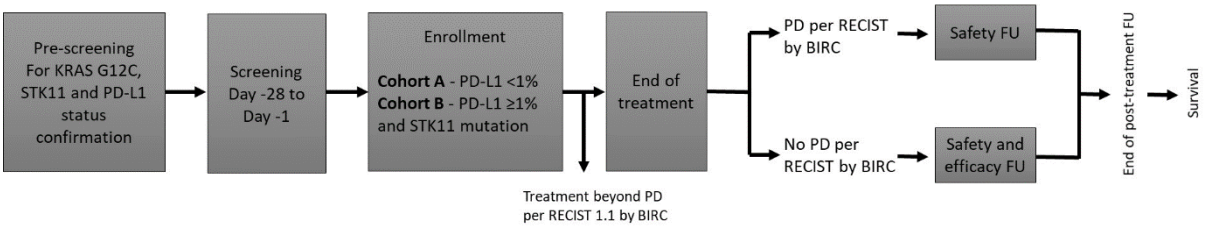
Additional survival assessments may be performed outside the 12-week follow-up schedules if a survival update is required due to safety or regulatory needs.

Survival information can be obtained via phone, and information will be documented in the source documents and relevant eCRFs. Information on the therapies received for NSCLC, if

any, after study treatment has been completed will be collected. All SAEs reported during this time period must be reported as described in Section 8.7.

Figure 7-1 illustrates study flow.

Figure 7-1 Study Flow



7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment and further protocol-required assessments or follow-up for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 1.3).

See Section 6.6 for information on continued access to study treatment after the end of the study

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

AND

- No longer wishes to receive study treatment

AND

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g., to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

7.5 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to)

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment (instructions will be provided to the Investigator for contacting the participant, when the participant should stop taking the drug and when the participant should come for a final visit). The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in Section 1.3. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

- Adherence to the study design requirements, including those specified in Section 1.3, is essential and required for study conduct.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Molecular pre-screening

All participants will be asked to sign and date an IRB/IEC approved "Molecular pre-screening informed consent form" before starting screening procedures (see Section 8.10).

In order to be considered eligible for the study, participants must have the following local or central (from a Novartis-designated central laboratory) test results:

- presence of the KRAS G12C mutation,
- known PD-L1 expression status
- presence of an STK11 mutation (for cohort B only).

For participants in China only: PD-L1 expression, KRAS G12C mutation status and STK11 mutation status (STK11 for cohort B only) must be determined by local assessment, according to criteria described below.

For local testing, results must be determined using a test which is validated according to local regulation at a Clinical Laboratory Improvement Amendments (CLIA)-certified USA laboratory or an accredited laboratory outside of the USA. Available information on the local assessment of KRAS G12C and STK11 mutations and PD-L1 expression status must be documented in the participant's medical record and will be collected during pre-screening. Participants who have local documentation of the status of all required biomarkers (KRAS G12C mutation and PD-L1 status for patients eligible to cohort A; KRAS G12C mutation, PD-L1 status and STK11 mutation for patients eligible for Cohort B) will be allowed to simultaneously sign the molecular pre-screening ICF and main ICF and begin screening procedures. These patients will be enrolled in the study on the basis of their local biomarker results after successful completion of the screening procedures.

Participants who do not have local documentation on the status of all required biomarkers must submit a tissue and/or blood sample for testing to the Novartis-designated central laboratory as part of pre-screening (after signature of the molecular pre-screening ICF) and prior to entering main screening. Participants will be allowed to sign the main ICF and begin screening procedures while waiting for the central test results which must be received prior to treatment, during the 28-day screening period (Section 8.2) and results may take up to 2 weeks (10 business days) once the sample is received at the Novartis-designated central laboratory. The pre-screening results from central testing for all tested participants (whether the participant is eligible or not for the study) will be communicated to the respective study center by the Novartis-designated central laboratory. The sample collection information must be entered on the appropriate sample collection log eCRF page(s) and requisition form(s). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to Investigators in a separate Laboratory Manual.

During pre-screening, information will be collected on local assessment of EGFR-sensitizing mutation status, ALK rearrangement status and/or other known druggable alteration information (if available).

KRAS G12C mutation status (all participants)

All participants must have a local or central (from a Novartis-designated central laboratory) tissue or blood-based test result that is positive for the presence of the KRAS G12C mutation to be eligible for the study.

For local testing, KRAS G12C mutation must be determined using a molecular test that detects mutations in DNA derived from tumor tissue or in circulating tumor DNA (ctDNA) derived from blood plasma. Immunohistochemistry results are not accepted.

Central testing for KRAS G12C mutation status will be done using investigational NGS tests that detect mutations in DNA derived from formalin fixed, paraffin-embedded tumor tissue or ctDNA derived from blood plasma at a Novartis-designated central laboratory. Participants who submit a blood sample for KRAS G12C mutation status determination can be enrolled based on the blood-based results, but site will be required to submit a tissue sample before enrollment for subsequent central analysis on tissue.

Participants with tissue sample submitted for KRAS G12C mutation status determination are required to submit a pre-screening blood sample any time before enrollment (in addition to the screening blood sample) for subsequent central analysis on blood. For participants whose plasma sample produces an inconclusive or negative KRAS G12C result, a FFPE tumor tissue sample should be reflexively tested for the presence of a KRAS G12C mutation during pre-screening due to lower mutation detection rates in ctDNA.

PD-L1 expression status (all participants)

For enrollment in cohort A, participants must have PD-L1 expression status <1% and for cohort B, PD-L1 expression status ≥1%, assessed by immunohistochemistry (IHC) in tumor tissue. This analysis could be either performed locally or centrally for enrollment.

For local testing, PD-L1 status must be determined according to tumor proportion score (TPS) by the PD-L1 IHC 22C3 or 28-8 pharmDx assays or tumor cell (TC) membrane expression by the Ventana PD-L1 SP263 assay.

Central testing for PD-L1 expression status will be done using the PD-L1 IHC 22C3 pharmDx or Ventana PD-L1 SP263 assay at a Novartis-designated central laboratory.

STK11 mutation status (cohort B only)

Cohort B participants must have a local or central (from a Novartis-designated central laboratory) tissue- or blood-based test result that is positive for the presence of an STK11 mutation to be eligible for the study.

For local testing, STK11 mutations must be determined using a molecular test that detects mutations in DNA derived from tumor tissue or in circulating tumor DNA (ctDNA) derived from blood plasma. Immunohistochemistry results are not accepted.

If local STK11 results are available, for patient eligibility purposes, the following are acceptable:

- STK11 loss of function mutations, including splice site mutations, nonsense mutations, frameshift mutations, and missense mutations as defined below
- Any splice alterations within the splice donor or acceptor site (defined as the first two or last two bases of the intron), any in-frame insertion or deletion affecting amino acids 49 – 309

Central testing for STK11 mutation status will use the same investigational (see Section 2.3) NGS tests that will be used for KRAS G12C mutation testing (described above). If STK11 status is centrally determined, the KRAS G12C status must also be confirmed by the Novartis central laboratory for eligibility.

Participants with tissue sample submitted for STK11 mutation status determination are required to submit also a pre-screening blood sample any time prior to treatment (in addition to the screening blood sample). Participants with a positive STK11-mutated blood result can be enrolled based on those results, but sites are required to submit a tissue sample during screening for subsequent central analysis. For participants with an inconclusive or negative STK11 mutation blood result, a tissue sample should be reflexively tested during pre-screening due to lower detection rates in blood.

Sample requirements (all participants)

As detailed in Section 8.9, a tumor tissue and blood sample must be submitted to the Novartis-designated laboratories for all participants, independently of the presence of local test results. The tumor tissue sample will be used for centralized PD-L1 expression, KRAS G12C mutation and/or STK11 mutation status determination for eligibility during pre-screening (for participants without local results) or for retrospective, central confirmation (for participants enrolled using qualified local results, samples are to be collected prior to study treatment initiation). A blood sample may be used for KRAS G12C mutation and/or STK11 mutation status determination for eligibility during pre-screening (for participants without local results) or for retrospective, central confirmation (for participants enrolled using qualified local results). The tissue and blood samples may also be used for development of one or more *in vitro* diagnostic tests, such as companion diagnostic test(s) and/or exploratory biomarkers.

Tumor tissue samples must contain 20% tumor content. Tumor tissue samples obtained from bone metastases and cytology samples are not acceptable.

Remaining tumor tissue from pre-screen failure samples will be returned if requested by the site. However, a small amount of any remaining tissue will be retained from all participants (both enrolled and pre-screen/screen failed), under control of Novartis, to support the potential development of *in vitro* diagnostic tests, such as companion diagnostic test(s). If the participant is enrolled, the remaining tissue will be kept at a Novartis-designated laboratory. If the site requests the tumor tissue to be returned, additional material will be retained for diagnostic development and exploratory analyses prior to returning the remaining tissue back to site. Additional tissue may be requested, retrospectively, if available, to support development of future companion diagnostic test if the remaining tissue sample is insufficient for analysis.

Blood samples from pre-screen failures will also be retained to support the potential development of *in vitro* diagnostic tests, such as companion diagnostic test(s).

8.2 Screening

All participants must provide a signed main ICF prior to performing any study specific procedures and will be evaluated for eligibility.

The screening assessments will be done within 28 days prior to the enrollment (Section 8). Laboratory parameters may be retested within the 28-day screening period for an individual participant if such parameters meet an exclusion criterion when initially tested.

Laboratory values obtained during the Screening period from the central laboratory will be used to assess participant's eligibility, except for China, where local laboratory results can be used for eligibility. If necessary, for immediate clinical decision locally unscheduled testing may be performed and used for eligibility.

Laboratory assessments performed as part of the screening evaluations will not be required to be repeated on the first day of dosing (except for hematology/chemistry and serum pregnancy test if not done within 72 hours prior to treatment start) unless considered clinically necessary by Investigator and/or required as per local institutional policies.

Imaging assessments will be performed at screening between Day -28 and Day -1. Imaging assessments already completed during the regular work-up of the participant within 28 days prior to start of treatment (-42 days for whole body scan), including before signing the main study ICF can be considered as the baseline images for this study. Any imaging assessments obtained after enrollment cannot be considered baseline images.

Participants who are enrolled in the IRT system and failed to start treatment, e.g. participants confirmed in IRT in error, will be considered as early terminators. The reason for early termination should be recorded on the appropriate eCRF.

8.2.1 Eligibility screening

When all screening procedures are completed and once the participant's eligibility has been checked and confirmed (i.e., all inclusion/exclusion criteria have been verified), the key eligibility criteria checklist will be completed prior to the first dose of study treatment in the IRT system by the Investigator or designee. The eligibility check will be embedded in the IRT system.

Please refer Section 6.3.1 and comply with detailed guidelines in the IRT manual.

8.3 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Data to be collected on participant characteristics at pre-screening include:

- Demography: age, sex, race/predominant ethnicity (if permitted). Participant race/ethnicity data should be collected wherever allowable by local laws and regulations. These data are collected and analyzed to identify any differences in the safety and/or efficacy profile of

the treatment due to these characteristics. In addition, these data are necessary to assess the diversity of the study population as required by Health Authorities.

- Cancer characteristics including diagnosis, history, extent of disease
- Information on tumor samples submitted to the central laboratory for testing
- PD-L1 status per participant's record (where available)
- KRAS G12C and STK11 mutation status per participant's record (where available)

Data to be collected on participant characteristics at screening include:

- Molecular alteration status of EGFR, ALK and other genes which are druggable, per participant's record
- Other background or relevant medical history/current medical conditions (until date of signature of informed consent) including smoking / vaping history
- Prior antineoplastic therapies (medications, radiation, surgeries), and date of progression/recurrence prior to study entry
- Tumor imaging assessment
- Other assessments to be completed for the purpose of determining eligibility (ECOG, PS, complete physical examination, vital signs, hematology, blood chemistry, coagulation, urinalysis, serum pregnancy test for women of child-bearing potential [only recorded in source documentation], 12-Lead ECG and Cardiac Imaging)
- Prior and current concomitant medications and surgical and medical procedures (All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.8 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF).

Data to be collected on participant characteristics at C1D1 (pre-dose) include:

- PRO assessments

8.4 Efficacy assessments

Planned time points for all efficacy assessments are provided in Section 1.3 Schedule of Activities.

8.4.1 Tumor assessment

Tumor response will be assessed both locally and centrally according to the Novartis guideline version 3.2 (Appendix 8 Section 10.8) based on RECIST 1.1 (Eisenhauer et al 2009).

The central review of the scans will be carried out in a blinded fashion. Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis (Details of the central review process will be described in the independent review charter).

Information regarding biopsy results, prior interventions (e.g., radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions should be transmitted to the imaging CRO with the baseline images for review by

the independent radiologist. Sites must transfer information as specified in the imaging CRO site manual and ensure the data is consistent with the data entered in the clinical database.

The CT scan component of the FDG-PET/CT should be used for treatment response assessment only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Section 10.8).

The imaging assessment collection plan is presented in Table 8-1.

Table 8-1 Imaging Assessment Collection Plan

Procedure	Screening/Baseline (within 28 days prior to start of treatment)	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)[#]	Mandated	**During Treatment:** Mandated, every 6 weeks (+/- 7 days) from C1D1 until Week 54, then every 12 weeks (+/- 7 days) until confirmed PD* **During Post Treatment Follow-Up:** participants with EOT reason other than disease progression, withdrawal of consent/opposition to use data/biological samples or death will continue to collect imaging and follow the same schedule of every 6 weeks (+/- 7 days) for the 54 weeks after C1D1, then every 12 weeks (+/- 7 days), thereafter until confirmed PD*
Brain MRI or CT	Mandated	**If brain metastases are present at baseline** **During Treatment:** Every 6 weeks (+/- 7 days) from C1D1 up to 54 weeks and every 12 weeks (+/- 7 days) thereafter until confirmed PD*. **During Post Treatment Follow-Up:** Participants with EOT reason other than disease progression, withdrawal of consent/opposition to use data/biological samples or death will continue to collect imaging and follow the same schedule proposed during treatment. **If no brain metastases are present at baseline** **During Treatment:** Every 12 weeks (+/- 7 days) from C1D1 until confirmed PD*. **During Post Treatment Follow-Up:** Participants with EOT reason other than disease progression, withdrawal of consent/opposition to use data/biological samples or death will continue to collect imaging and follow the same schedule proposed during treatment. Otherwise, if clinically indicated
Whole body bone scan (Per institutional standard of care [e.g., Tc-99m bone scan, whole body bone MRI, 18F - fluorodeoxyglucose positron emission tomography (FDG-	Mandated (within 42 days prior to start of treatment)	If clinically indicated.

Procedure	Screening/Baseline (within 28 days prior to start of treatment)	During Treatment/Follow-up
PET) or 18 F - sodium fluoride (NaF) PET])		
Localized bone CT, MRI, or x-ray	Mandated for any lesions identified on the whole-body bone scan that are not visible on the chest, abdomen, and pelvis CT or MRI.	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis. Otherwise, if clinically indicated
Color photography (with scale/ruler)	If clinically indicated,in case skin metastatic lesions are present.	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis. Otherwise, if clinically indicated
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis. Otherwise, if clinically indicated
*Progression by RECIST 1.1 as confirmed by BIRC. # Combined Positron Emission Tomography (PET)/CT may be used for treatment response assessment if the CT component is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media.		

Baseline imaging assessments

Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to start of treatment (42 days for whole body bone scan), including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after C1D1/enrollment cannot be considered baseline images. The following assessments are required at screening/baseline:

- Chest, abdomen, and pelvis CT or MRI (Combined Positron Emission Tomography (PET)/CT may be used if the CT component is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media)
- Brain MRI or CT
- Whole body bone scan
- Localized bone CT, MRI, or x-ray, for any lesions identified on the whole-body bone scan that are not visible on the chest, abdomen and pelvis CT or MRI
- Color photography for any skin metastatic lesions present, if clinically indicated
- CT or MRI of other metastatic sites (e.g., neck), if clinically indicated

If a participant is known to have a contraindication to CT intravenous (IV) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts; however, if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed.

Brain MRI or CT should be completed. Contrast enhanced brain MRI is preferred. However, if MRI contrast is contraindicated, then MRI without contrast or CT with contrast are acceptable.

A whole-body bone scan should be performed per institutional standard of care [e.g., Tc-99m bone scan, whole body bone MRI, 18F- fluorodeoxyglucose positron emission tomography

(FDG-PET) or 18 F-sodium fluoride (NaF) PET]. Localized CT, MRI, or X-rays should be acquired for all skeletal lesions identified on the screening whole body bone scan which are not visible on the chest, abdomen and pelvis CT/MRI.

If clinically indicated, CT or MRI of other areas (e.g., neck) of disease should be performed.

If skin metastatic lesions are present at screening, color photography should be acquired (if clinically indicated) using a digital camera in clear focus, including a scale/ruler, in such a way that the size of the lesion(s) can be determined from the photograph.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Chest x-rays and ultrasound should not be used to measure tumor lesions.

Post-baseline imaging assessment

Imaging assessments as described in Table 1-3 and Table 8-1 should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing.

Imaging assessments should be scheduled using the date of first dose (C1D1) as the reference date (not the date of the previous tumor assessment), and this schedule should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments performed.

Additional imaging assessments may be performed at any time during the study at the Investigator's discretion to support the efficacy evaluations for a participant, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Time points at which progression is determined locally

For participants who have disease progression determined by the local Investigator, an expedited central review is required. Rapid image transmission to the imaging CRO should be accomplished by transferring the images electronically. In all instances, the process at the imaging CRO will ensure that the central reviewers remain blinded to the results of the local assessment and the expedited nature of the review. The Investigator seeking an expedited review must indicate this request to the imaging CRO at the time of image submission. The imaging will undergo expedited central review (within 5 business days from the time of image receipt at the imaging CRO and once all applicable queries are resolved) and the results of the central review will be communicated to the site. While the Investigator is awaiting the results

of the central review, it is preferable that the participant continues on study treatment. However, during this time, the Investigator should do whatever is medically necessary for the participant.

If the central review confirms disease progression, then the participant will discontinue study treatment and subsequent tumor assessments are no longer required unless the criteria are met to continue study treatment beyond disease progression per RECIST 1.1 (for participants treated with JDQ443 only) as described in Section 6.1.4.1.

If the central review does not confirm disease progression, the participant should continue receiving the study treatment until disease progression has been confirmed by BIRC at a subsequent visit or, as a minimum requirement, until at least one additional tumor assessment has been completed, unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy.

In summary, for expedited timepoints (assessed as progressive disease by local):

Rapid image transmission to the central imaging CRO may be accomplished by uploading all digital images acquired by the Investigator in a secured website, while preserving the blinded status of the images.

- If central radiology confirms progressive disease, the study site will be informed. This participant should then discontinue study treatment. Participants treated with JDQ443 may continue study treatment beyond disease progression per RECIST 1.1 if according to investigator's judgement the participant is benefiting from study treatment and if certain conditions are met, as described in Section 6.1.4.1.
- If central radiology does not confirm progressive disease, the study site will be informed. As long as it is clinically acceptable, every effort should be made to continue the participant on study treatment until progressive disease is confirmed by BIRC or for at least one subsequent radiological timepoint.

Time points without locally determined progression

All imaging time points without locally determined progression will be read on an ongoing, non-expedited basis as detailed in the imaging manual to be provided by the designated imaging CRO and independent review charter. Results of these readings will not be communicated to the sites.

Treatment beyond disease progression

Following determination of disease progression, if the Investigator believes the participant treated with JDQ443 may derive benefit from continuing study treatment, the participant will be permitted to continue treatment beyond initial disease progression as per RECIST 1.1 by BIRC. Please see Section 6.1.4.1 for additional information.

Efficacy follow-up imaging assessments

For participants who discontinue treatment for reasons other than initial disease progression as per RECIST 1.1, tumor assessments must continue to be performed as outlined in Table 1-3 regardless if participants start on new antineoplastic therapy before documented disease progression. Please refer to Section 8.4 for additional information.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, the collection of images (e.g., change of imaging center or imaging frequency) may be modified by Novartis and will be communicated to the Investigator.

8.4.2 Appropriateness of efficacy assessments

Tumor assessments performed every 6-12 weeks of study treatment are consistent with the standard clinical practice for patients with advanced NSCLC. Conducting tumor evaluations more than 6 weeks apart may expose a participant to an unnecessary treatment if the disease progression event takes place between the infrequent assessments or prevent early identification of progression and appropriate treatment.

8.5 Safety assessments

Safety assessments are specified below with Section 1.3 detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 8.7

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 3 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-2 Physical Assessments

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and complete neurological examination. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Complete physical examination will be performed at screening, C1D1 and at EOT.. A direct and oriented physical exam including the examination of general appearance, vital signs (blood pressure [SBP and DBP] and pulse) and complete neurological examination will be performed at all visits starting from C2D1 as per Table 1-3 except where a complete physical examination is required (see above). Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include blood pressure (supine position preferred when ECG is collected), pulse measurement, respiratory rate and body temperature. They will be measured at screening and at subsequent timepoints as specified in Table 1-3.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but preferably without shoes) will be measured as specified in Table 1-3 .
ECOG performance status	ECOG performance status will be measured at screening and at subsequent time points as specified in Table 1-3 .

ECOG performance status scale will be used as described in Table 8-3 (Oken et al 1982).

Table 8-3 ECOG Performance Status

Grade	ECOG performance status
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 house work, 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

8.5.1 Physical examinations

Physical examination should be performed as specified in Table 8-2 .

8.5.2 Vital signs

Vital signs should be monitored according to the instructions in Table 8-2 .

8.5.3 Electrocardiograms

Electrocardiograms (ECGs) will be centrally evaluated and must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling, and any remaining assessments for that visit.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions, e.g., at Screening to assess eligibility. The Investigator must calculate corrected QT interval (QTc) if it is not auto-calculated by the ECG machine.

ECGs will be performed at screening, C1D1, C1D15 and at EOT (Table 8-4).

Triplicate 12 lead ECGs are to be recorded approximately 2 minutes apart. The mean QTc value for each visit will be calculated from the triplicate ECGs for each participant.

Table 8-4 Central ECG collection plan

Cycle	Day	Time	ECG Type
Screening		Anytime (before C1D1)	12 Lead, triplicate
1	1	Pre-dose and 4 hours post-dose (within 15 minutes prior to PK)	12 Lead, triplicate
1	15	Pre-dose and 4 hours post-dose (within 15 minutes prior to PK)	12 Lead, triplicate
EOT		Anytime	12 Lead, triplicate
Unscheduled or Unplanned ECG		Anytime if clinically indicated	12 Lead, triplicate

In order to enable ECG evaluation by the central ECG laboratory for eligibility assessment, ECGs should be submitted to the central ECG laboratory prior to enrollment (to refer to the ECG manual for the turn around time).

In the event that a QTcF value of > 500 ms is observed or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched PK sample and record the time

and date of the last study treatment intake to determine the drug exposure. Dose adjustments in case of QT prolongation should be performed per Section 6.5.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms), a copy of the assessment is sent to the central ECG laboratory for expedited review and the ECG is repeated at the site to confirm the diagnosis. If the participant is hemodynamically compromised, the Investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

All ECGs, including unscheduled safety ECGs with clinically relevant findings collected during the study need to be transmitted to the central ECG laboratory for review.

The original ECGs on non-heat sensitive paper or a certified copy on non-heat sensitive paper and appropriately signed must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or adverse events as appropriate.

8.5.3.1 Cardiac imaging - echocardiogram or cardiac magnetic resonance (CMR)

Echocardiogram or CMR to assess LVEF will be performed at screening, C2D1, at EOT and as clinically indicated.

This assessment will be performed locally. The modality of the cardiac function assessments must be consistent throughout the study i.e., if echocardiogram is used for the baseline assessment then echocardiogram should also be used for subsequent scans. The participant should also be examined using the same machine and operator whenever possible.

8.5.3.2 Cardiac enzymes

Creatine kinase (CK) assessment has to be performed at the same schedule as the other blood biochemistry tests. Isoenzyme (CK-MB) and Troponins (I and/or T) will be performed if clinically indicated by the Investigator (refer to Table 8-5).

8.5.4 Clinical safety laboratory tests

All laboratory parameters assessed for safety purposes (Table 8-5) will be evaluated centrally except for urinalysis (dipstick for macroscopic panel) and urine pregnancy tests (dipstick) that will be performed locally. In the case of any macroscopic out of range parameters, a urine sample will be sent to central laboratory for further analysis (microscopic panel). Dipstick for urinalysis test (macroscopic panel) and dipstick for urine pregnancy test will be performed unless local institution policies dictate otherwise. For China only, local laboratories can be used for all specimens collected (i.e, central laboratory assessments not mandatory).

Samples for these parameters will be collected prior to study treatment administration.

Local laboratory assessments may be performed if medically indicated or when the treating physician cannot wait for central laboratory results for decision making. In this particular situation, the blood sample obtained at the same time point should be submitted to the central laboratory for analysis in parallel with local analysis.

The results of the local laboratory will be recorded in the eCRF if the following criteria are met:

- A treatment decision was made based on the local results, or
- There are no concomitant central results available.

Laboratory values obtained during the Screening period from the central laboratory will be used to assess participant's eligibility.

The site does not need to wait for the results of centrally-analyzed laboratory assessments when an immediate clinical decision needs to be made (e.g., confirmation of eligibility, study treatment interruption, re-initiation, and/or termination) and in those cases locally unscheduled testing may be performed and used for eligibility assessments.

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the Laboratory Manual.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

Table 8-5 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Erythrocytes, Leukocytes, Erythrocyte Cell Morphology (if possible), Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils in percentage or absolute)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphate, Sodium, Potassium, Creatinine, Creatinine clearance, Total Bilirubin, Direct Bilirubin (only if total bilirubin is ≥ grade 2), Blood Urea Nitrogen (BUN) or Urea, Serum Amylase, Lipase, Fasting Glucose (non-fasting allowed post-baseline), Bicarbonate, Chloride, Creatine Kinase (CK) Uric Acid at screening and thereafter if clinically indicated
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Microscopic Panel if indicated, (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells)
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Liver event testing and liver follow-up testing	To refer to Section 10.5 (Liver safety monitoring)
Renal follow-up	To refer to Section 10.6 (Renal safety monitoring)
Pregnancy Test and assessment of fertility	Serum / Urine pregnancy test. If local requirements dictate otherwise, local regulations should be followed. Confirmatory serum pregnancy required in case of positive urine pregnancy test. Urine pregnancy test will be performed locally. Follicle Stimulating Hormone (FSH),

Test Category	Test Name
	Luteinizing Hormone (if required to confirm the menopausal status): these tests will be performed locally and documented in source document. At screening a serum pregnancy test is to be performed within 72 hr before the first dose, while during the study (Day 1 of each cycle) urine pregnancy tests are sufficient. An End of Treatment serum pregnancy test is also required to be performed. For women considered to be post-menopausal and not of childbearing potential, pregnancy testing is not required. If a serum pregnancy test is required as per local practice at day 1 of every cycle, the urine pregnancy test does not need to be repeated.
Cardiac enzymes	Isoenzyme (CK-MB) and Troponins (I and/or T) if clinically indicated.

8.5.5 Pregnancy testing

A condom is required for all sexually active male participants to prevent them from fathering a child and to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm and female participants should not donate oocytes for at least 7 days post discontinuation of study treatment.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

All women of child-bearing potential will have a serum pregnancy test within 72 hours prior to the first dose of study treatment. hCG may also be considered a tumor marker, therefore if hCG levels are detected, another blood sample at least 4 days later must be taken to assess the kinetics of the increase, and a transvaginal ultrasound must be performed to rule out pregnancy. Urine pregnancy tests will be required to be performed on Day 1 of every cycle beginning with Cycle 2, followed by serum pregnancy test at the end of treatment visit. Women of child-bearing potential will be instructed to contact the site immediately at any time during the study (on-treatment or during follow-up) should they have a positive pregnancy test.

In case of positive urine pregnancy testing, additional testing must be performed to confirm the pregnancy, and, if confirmed, follow the reporting requirements as described in Section 8.7.4.

A positive pregnancy test requires immediate discontinuation of study treatment. If a positive pregnancy test is performed in between study visits, the participant must immediately notify the Investigator. Male participants must notify the Investigator in case their partner is confirmed with positive pregnancy test results during the treatment period. See Section 8.7.4 for pregnancy reporting.

Local pregnancy test and associated results will not be collected on the eCRF.

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be shipped or provided directly to participants (e.g., together with the study treatment). Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the Investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

When non-child-bearing potential status is determined during the study, further pregnancy testing will not be continued. For further details on the assessment of fertility, please refer to the study exclusion criteria in Section 5.2.

If local requirements dictate otherwise, local regulations should be followed.

8.5.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population. The inclusion / exclusion criteria, dose modification guidelines, and safety assessments in this trial account for both the disease indications and the available safety data for JDQ443 [JDQ443 Investigator's Brochure].

8.6 Additional assessments

8.6.1 Clinical Outcome Assessments (COAs)

The PRO measures in this study have been included to assess the effects of the study treatment on participants' lung cancer symptoms, functioning and other areas of health-related quality of life (QoL). These include the following:

The Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) is a 7-item, patient-reported outcome measure which assesses patient-reported symptoms associated with advanced NSCLC. It contains five domains and accompanying items that were identified as symptoms of NSCLC: cough (1 item), pain (2 items), dyspnea (1 item), fatigue (2 items), and appetite (1 item). The NSCLC-SAQ has been developed in patients with NSCLC including both males and females, varying levels of age, race, education, marital status, and ECOG performance status, and has been qualified by the US Food and Drug Administration as a measure of lung cancer symptoms (McCarrier et al 2016).

The European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30) is a questionnaire developed to assess the health-related quality of life of cancer patients. The questionnaire contains 30 items and is composed of both multi-item scales and single-item measures based on the participants experience over the past week. These include five domains (physical, role, emotional, cognitive and social functioning), three symptom scales (fatigue,

nausea/vomiting, and pain), six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) and a global health status/QoL scale. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a higher level of functioning; a high score for the global health status represents a high health-related quality of life (HRQoL), but a high score for a symptom scale represents a high level of symptomatology. All scorings will follow the scoring procedures defined by the EORTC Scoring Manual (Fayers et al 2001).

The National Cancer Institute (NCI) Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) was developed to evaluate patient-reported tolerability in cancer clinical trial participants. The PRO-CTCAE characterizes the frequency, severity, interference, and presence/absence of symptomatic adverse events that can be meaningfully reported from the patient perspective. For this study, a subset of eight items were selected that represent possible adverse experiences from common oncology drugs and medications of this drug class that are not covered adequately in other PRO questionnaires (Kluetz et al 2016).

In order to ascertain the overall burden of the side effect profile, the single item, GP5, of the Functional Assessment of Cancer Therapy-General (FACT-G) will be included to assess global side effect impact. Together with the PRO-CTCAE these items will help us to better understand the patient-reported experience of benefits versus risks of the treatment and impact over the treatment course (Pearman et al 2018).

The Patient Global Impression of Severity of Symptoms questionnaire (PGIS) asks the study participant about overall severity of lung cancer symptoms and will be used as a tool to assess clinical meaningfulness of symptom change in participants during the study (FDA Core PROs in Cancer 2021).

The EQ-5D-5L is a generic instrument for describing and valuing health. It is based on a descriptive system that defines health in terms of 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension has five response categories corresponding to no problems, some problems, and extreme problems. The instrument is designed for self-completion, and respondents also rate their overall health on the day of the interview on a 0–100 hash-marked, vertical visual analogue scale (EQ-VAS). The EQ-5D has been adopted as a tool to calculate health utilities for the purpose of cost-effectiveness analyses to present to health technology assessment agencies (Herdman et al 2011).

PRO data will be collected by self-report using an electronic device during the treatment, efficacy follow-up (if applicable) and survival periods. Participants will be given the opportunity to complete PRO questionnaires at site or at home before arriving at the site on scheduled visit days. Completion at home must be performed within 3 days before the scheduled visit (for more details, refer to vendor manual).

The following back-up options are available during the treatment period, efficacy follow-up (if applicable) and survival period for participants who might not return to the clinic: PRO completion can be done from home using a web-based application or by interview over the phone provided the interviewer has received the appropriate training on recording the participant's responses. These are only to be used if there is a valid reason for employing them

such as public health emergency, or patient unable to complete on provisioned device/web-based application (for more details, refer to vendor manual).

The NSCLC-SAQ, EORTC QLQ-C30, FACT GP5, PRO-CTCAE, PGIS-NSCLC and EQ-5D-5L PROs will be administered as indicated in Table 1-3 while the participant is on treatment, at EOT visit, during the post-treatment efficacy follow-up period (at corresponding imaging efficacy follow-up visits, if the participant is still followed for efficacy) and during the survival period.

- For participants who have discontinued study treatment due to progressive disease by RECIST 1.1 as assessed by BIRC and enter the safety and survival follow-up periods, NSCLC-SAQ, EORTC QLQ-C30, FACT GP5, PRO CTCAE, PGIS-NSCLC and EQ-5D-5L will be collected at EOT and every 12 weeks post progressive disease for a minimum of 3 timepoints.
- For participants, who continue study treatment beyond progressive disease by RECIST 1.1 as assessed by BIRC, PROs will continue to be collected at the same timepoints as defined during the treatment period. Once the participants discontinue study treatment and enter safety and survival follow-up periods, NSCLC-SAQ, EORTC QLQ-C30, FACT GP5, PRO CTCAE, PGIS-NSCLC and EQ-5D-5L will be collected at EOT and every 12 weeks post progressive disease for a minimum of 3 timepoints.
- For participants who have discontinued study treatment for any other reason than progressive disease by RECIST 1.1 as assessed by BIRC and enter the efficacy follow-up period, PROs will be collected at EOT and every 12 weeks for NSCLC-SAQ, EORTC QLQ-C30, FACT GP5, PRO CTCAE, PGIS-NSCLC and EQ-5D-5L and at the time of progressive disease by RECIST 1.1 as assessed by BIRC. Following progressive disease by RECIST 1.1as assessed by BIRC, NSCLC-SAQ, EORTC QLQ-C30, FACT GP5, PRO CTCAE, PGIS-NSCLC and EQ-5D-5L will be collected every 12 weeks post progressive disease for a minimum of 3 timepoints.

All PRO assessments should be administered in the participant's local language, at the scheduled visit (if not completed at home), prior to any tests, treatments, or receipt of results from any test, to avoid biasing the participant's perspective. Participant's refusal to complete all or any part of a PRO measure should not be captured as a protocol deviation. Participant questionnaires should be completed in the language most familiar to the participant.

The participant should be given sufficient space and time to complete the PRO measure(s), should be made aware that completed measure(s) are not reviewed by the Investigator/ study personnel and that they should report any discomfort, unusual symptoms or medical problems directly to the Investigator/ study personnel, according to the ICF.

If PRO questionnaires are completed by participant, and study treatment is delayed, actions will be taken according to scenarios listed in Table 8-6:

Table 8-6 PRO completion schedule if study treatment is delayed/rescheduled

Treatment delay length of time	PROs COMPLETED prior to re-scheduled visit?	Ask patient to complete PROs at rescheduled visit?
≤ 7 days,	YES	**Do *not* ask participants to complete the PROs again**
	NO	Ask participants to complete PROs for re-scheduled visit
> 7 days,	YES	Ask participant to complete PROs *again* for re-scheduled visit
	NO	Ask participant to complete PROs for re-scheduled visit

As per Section 4.5, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, study site staff may administer the questionnaires to the participants via interview over the phone (for more details, refer to the vendor manual).

8.7 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual contact will occur at least every 3 weeks (± 3 days) as per the visit scheduled, or more frequently if needed for safety monitoring and discussion of the participant´s health status until the participant can again visit the site. Events qualifying for being reported in the eCRF (e.g., AE, infection) should be entered as appropriate.

When a negative urine test is required for continued IMP administration, if participants cannot visit the site to have serum pregnancy tests done, urine pregnancy test kits may be shipped or provided directly to participants (e.g., together with the study treatment). The participant will be instructed by the site on their requirements to perform these urine pregnancy tests remotely and the communication process with site prior to participant self-administration (refer to Section 8.5.5 for details).

Depending on local regulations and capabilities, study site staff or Home Nursing Services may visit the participant at home to draw blood/urine samples if needed. Alternatively, safety lab tests and ECGs performed locally (e.g., by the participant's general practitioner or at another facility) will be allowed as appropriate.

8.7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign, including abnormal laboratory findings, symptoms or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participant and identifying AEs. Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

For participants who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 8.7.2 and are reported to be causally related with study procedures (e.g., an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured as adverse events.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.7.2):

AEs will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE V5.0). If CTCAE grading does not exist for an AE, the severity of mild, moderate, severe, life-threatening, and fatal corresponding to grades 1 - 5, will be used. Information about any deaths (related to an AE or not) will also be collected through a Death form.

1. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.
2. Its duration (start and end dates) or if the event is ongoing, and an outcome of not recovered/ not resolved must be reported.
3. Whether it constitutes a SAE (see Section 8.7.2 for definition of SAE) and which seriousness criteria have been met.
4. Action taken regarding study treatment. All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/permanently discontinued
   - Its outcome: recovery status or whether it was fatal

If the event worsens, then the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 AEs only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of main informed consent should be recorded in medical history of the participant.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (.e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST 1.1), should not be reported as a SAE, except if the Investigator considers that progression of malignancy is related to study treatment (Note: If more stringent, local regulations regarding reporting criteria and timelines prevail).

AEs separate from the progression of malignancy (i.e., deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Further information about adverse drug reactions for JDQ443 can be found in the [JDQ443 Investigator's Brochure].

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

8.7.2 Serious adverse events

An SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- Fatal
- Life-threatening

Note: life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect or results in fetal death
- Is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Social reasons and respite care in the absence of any deterioration in the participant's general condition
  - Treatment of an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

Medical and scientific judgment should be exercised in deciding whether other situations should be considered SAEs, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are 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 dependency or abuse (please refer to the [ICH-E2D Guidelines]).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered SAEs irrespective if a clinical event has occurred.

8.7.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting criteria and timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

Information about all SAEs is collected and recorded on the electronic Serious Adverse Event (eSAE) form (with paper backup if eSAE is unavailable); all applicable sections of the form must be completed in order to provide a clinically thorough report.

For participants who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF and will only be reported if the event is suspected to be causally related to a study procedure as assessed by the Investigator (e.g., an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant

improvement or stabilization. If the main ICF is not signed (e.g., molecular pre-screen failure), SAE collection ends 30 days after the last study related procedure.

For participants who failed the molecular pre-screening or screening, SAEs will be collected until the time the participant is deemed a molecular pre-screening or screen failure.

For participants who are enrolled, SAEs will be collected until 30 days after the participant has discontinued or stopped study treatment.

Any SAEs experienced after the 30 days period following the last administration of the study treatment should only be reported to Novartis if the Investigator suspects a causal relationship to the study treatment, unless otherwise specified by local law/regulations.

Progression of malignancy (including fatal outcomes), should not be reported as a serious adverse event, except if the Investigator considers that the progression is related to study treatment (Note: If more stringent, local regulations regarding reporting criteria and timelines prevail).

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting criteria and timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the [JDQ443 Investigator's Brochure] (new occurrence) and is thought to be related to the study treatment, a PS & PV Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees (EC) in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

8.7.4 Pregnancy

If a female trial participant becomes pregnant, the study treatment must be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence.

However, pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

The pregnancy should be followed up at 1, 3 and 12 (for a live birth only) months after the estimated date of delivery to determine outcome, including spontaneous or voluntary

termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Patient Safety & Pharmacovigilance (PS&PV). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.7.5 Disease-related events and/or disease related outcomes not qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with NSCLC, and can be serious/life threatening:

- Disease progression
- Lack of efficacy
- Death (related to study indication)

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE (Note: If more stringent, local regulations regarding reporting criteria and timelines prevail).

8.8 Pharmacokinetics

Serial blood samples will be collected from all participants to characterize the pharmacokinetics of JDQ443 at the visits defined in Section 1.3 (Schedule of Activities). In addition, residual samples used for PK and biomarker analyses may also be used for exploratory PK or PK/PD analysis. This could include using leftover plasma samples for protein binding analysis, metabolite profiling, other biomarker or bioanalytical purposes (e.g., cross validation between different sites, stability assessment), or other assays if there is sufficient sample remaining.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. Collection of PK samples may be stopped upon decision of the Sponsor, (i) if/when sufficient data are collected, (ii) after the primary CSR cut-off date is reached, or (iii) following decision to halt enrollment.

JDQ443 concentration data will be listed by study cohort, participant, and visit/sampling time point using SAS. Descriptive summary statistics will be provided by study cohort and visit/sampling time point using PAS. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

8.8.1 Pharmacokinetic blood collection and handling

PK blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein at the visits defined in the pharmacokinetic log (Table 8-7 or Table 8-8). Refer to the laboratory manual for detailed instructions regarding sample collection, numbering, processing and shipment.

Complete dosing and blood sampling information, including the date/time of actual blood draw and date/time of the last study treatment dose prior to the sampling, should be obtained on all sampling days and recorded on the PK eCRF. Time of vomiting, if it occurs within 4 hours following investigational drug(s) administration, should be documented in eCRF. Meal date/time before and after JDQ443 administration should be collected on the PK collection days.

An unscheduled PK blood sample will be collected, 1) if a participant experiences an AE suspected to be related to study treatment that results in an unscheduled visit or fits the criteria of an SAE, 2) whenever an unscheduled post-baseline tumor sample is collected during the treatment.

The date and time of the unscheduled blood sample collection, and the date, time and dose of the investigational drug taken prior to the unscheduled blood sample collection should be entered in the appropriate eCRF.

On days and time points where blood PD samples are to be drawn, the PK sample should be drawn first. On days and time points where ECG are collected, take ECG prior to PK blood draw.

For approximately 10 participants in each of the Cohorts (A and B), PK blood samples will be collected at time-points described in Table 8-7 (Intensive PK sampling scheme). Approximately 2 participants from this intensive PK group will be from China. For the remaining participants in each of the Cohorts (A and B), standard PK blood samples will be collected at time-points described in Table 8-8 (standard PK sampling scheme).

Table 8-7 PK blood collection log for JDQ443 treatment (intensive sampling; for approximately 10 participants in Cohort A and approximately 10 participants in Cohort B)

Treatment Period or Cycle	Day	Scheduled Time Point	Dose reference ID	Sample number	Analyte
1	1	CCI hour* /pre-dose	11	101	JDQ443
1	1	hour (± 30 minutes)	11	102	JDQ443
1	1	hour (± 30 minutes)	11	103	JDQ443
1	15	hour* /pre-dose	12 / 121[#]	104	JDQ443
1	15	hour (±10 minutes)	12	105	JDQ443
1	15	hours (±15 minutes)	12	106	JDQ443
1	15	hours (±15 minutes)	12	107	JDQ443
1	15	hours (± 30 minutes)	12	108	JDQ443
1	15	hours (± 30 minutes)	12	109	JDQ443
1	15	hours (± 30 minutes)	12	110	JDQ443
1	15	CCI hours (± 2 hours)/pre-evening dose)	12 / 122[&]	111	JDQ443

3	1	CCI hour*/pre-dose	13 / 131#	112	JDQ443
5	1	hour*/pre-dose	14 / 141#	113	JDQ443
7	1	hour*/pre-dose	15/ 151#	114	JDQ443
--	--	At time of on-treatment tumor sample collection**	--	115	JDQ443
--	--	Unscheduled***	--	1001+	JDQ443

*Collect samples immediately prior to the administration of study treatment.
These 3-digit dose reference ID refers to the dose taken prior to the corresponding PK sample.
& These 3-digit dose reference ID refers to the dose taken after the corresponding PK sample.
**if the scheduled biopsy sample collection is postponed for any reason, a PK sample is to be collected at the time of the biopsy collection.
***Collected if a participant experiences an AE suspected to be related to study treatment that results in an unscheduled visit or fits the criteria of an SAE. Unscheduled PK sample may be collected at any time if clinically indicated, and must be sequentially numbered as 1001, 1002, 1003, etc..
Note: PK sample to be prioritized over the biopsy sample collection (optional tumor biopsy)

Table 8-8 PK blood collection log for JDQ443 treatment (standard sampling; remaining participants in Cohort A and Cohort B)

Treatment Period or Cycle	Day	Scheduled Time Point	Dose reference ID	Sample number	Analyte
1	1	CCI hour* /pre-dose	11	101	JDQ443
1	1	hour (± 30 minutes)	11	102	JDQ443
1	1	hour (± 30 minutes)	11	103	JDQ443
1	15	hour* /pre-dose	12/121#	104	JDQ443
1	15	hours (±30 minutes)	12	108	JDQ443
1	15	hours (± 30 minutes)	12	109	JDQ443
3	1	hour*/pre-dose	13/131#	112	JDQ443
5	1	hour*/pre-dose	14/141#	113	JDQ443
7	1	hour*/pre-dose	15/151#	114	JDQ443
--	--	t time of on-treatment tumor sample collection**	--	115	JDQ443
--	--	Unscheduled***	--	1001+	JDQ443

*Collect samples immediately prior to the administration of study treatment.
These 3-digit dose reference ID refers to the dose taken prior to the corresponding PK sample.
**: If the scheduled biopsy sample collection is postponed for any reason, a PK sample is to be collected at the time of the biopsy collection.
***Collected if a participant experiences an AE suspected to be related to study treatment that results in an unscheduled visit or fits the criteria of an SAE. Unscheduled PK sample may be collected at any time if clinically indicated, and must be sequentially numbered as 1001, 1002, 1003, etc.
Note: PK sample to be prioritized over the biopsy sample collection (optional tumor biopsy)

8.8.2 Analytical method

Concentrations of JDQ443 in human plasma will be determined with a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay.

Concentrations below the lower limit of quantification (LLOQ) will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

8.9 Biomarkers

Biomarker analyses in tumor and/or in blood will be used to investigate the CCI and to determine CCI

CCI [redacted]. In addition, CCI [redacted], as well as CCI [redacted] may be explored. Samples and data may be also used to CCI [redacted].

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made by Novartis to stop a biomarker collection or to not perform or discontinue analysis based on emerging data and/or due to practical or strategic reasons.

During the study, both blood and tumor samples will be collected to perform exploratory biomarker assessments as detailed in Table 8-9 , depending on sample availability, resources, participants' outcomes and as new scientific evidence or alternative methods become available (e.g., as indicated by new findings from the literature as well as from Novartis internal data). If a particular assay is not available for samples collected in a particular region/country, sample collection and/or analysis may be omitted.

For participants in China only, the collection of biomarker samples or the collection type or amount may vary, conditional upon approval from local authorities (including but not limited to HGRAC).

The sample collection information must be entered on the appropriate sample collection eCRF page(s) and requisition form(s). Detailed instructions for the collection, processing, and shipment of biomarker samples are outlined in the laboratory manual for the study. Sample(s) should be collected at the visit/time point(s) defined in the biomarker Table 8-9 .

Table 8-9 Biomarker sample collection plan

Sample Type	Volume	Visit	Timepoint
Tumor and Blood Samples at Pre-Screening*			
Mandatory for eligibility** Tumor sample for PD-L1 expression, KRAS G12C mutation and STK11 mutation (cohort B only) status assessment (participant eligibility) and diagnostic development	FFPE tissue block (preferred) or 16 to 20 freshly cut, 5 µm tissue sections	Pre-screening *Molecular pre-screening requires participant's written consent on the molecular pre-screening ICF.*	Samples to be submitted prior to main screening - participants who have locally assessed PD-L1 expression status, KRAS G12C mutation and STK11 mutation (cohort B only) status, may directly enter main screening in parallel to sending the tumor samples
Mandatory** Blood plasma to determine KRAS G12C mutation and STK11 mutation status May be used to determine eligibility where local results are not available	2 × 10 mL whole blood	Pre-screening *Molecular pre-screening requires participant's written consent on the molecular pre-screening ICF.*	Prior to main screening
Tumor Samples in Treatment Period*			
Mandatory, where available*** Tumor	Archival FFPE block (preferred) or 6 to 10	C1D1	Any time prior to treatment

Sample Type	Volume	Visit	Timepoint
sample for exploratory analysis	freshly cut, 4 to 5 µm tissue sections		
Optional Newly obtained tumor biopsy for exploratory analysis (requires optional biopsy consent within the main ICF)	3-6 passes core needle biopsy as formalin fixed tissue or FFPE block	C1D1	Prior to start of treatment - Biopsy may be performed during screening to accommodate patient scheduling
		C1D15	4 and 8 hours post-dose
		EOT/PD	At EOT if EOT=PD or at the time of first disease progression, prior to the initiation of the new anti-cancer therapies
Blood samples in Screening and Treatment Period*			
Mandatory Blood plasma sample for KRAS G12C/STK11 assessment and diagnostic development	2 × 10 mL whole blood	Screening	Day -28 to D-1
Mandatory Blood plasma sample for exploratory cfDNA analysis	2 × 10 mL whole blood	C1D1	Pre-dose
		C1D15	Pre-dose
		C2D1	Pre-dose
		C3D1	Pre-dose
		D1 of every 2 cycles thereafter	Pre-dose
		EOT	EOT
Mandatory Blood plasma for exploratory analysis of CCI [redacted]	1 × 3 mL whole blood	C1D1	Pre-dose
		C1D15	Pre-dose
		C3D1	Pre-dose
		EOT	EOT

* For participants in China only: PD-L1 expression, KRAS G12C status and STK11 mutation status (cohort B only) must be determined by local assessment . Biomarker sample collection is conditional upon approval from local authorities (including but not limited to HGRAC).
** Tissue and blood samples are required from all participants as a part of pre-screening. For cases where documented local results from a qualified laboratory are not available and the central test results will be used for eligibility testing based on PD-L1 expression in tissue, KRAS G12C mutation status and STK11 mutation status (cohort B only) in tissue or blood, the sample must be submitted as part of pre-screening. While awaiting results, patient may proceed to main screening, however results must be received with appropriate biomarker status prior to starting treatment (Section 5.1 and Section 8.1). With documented local results for all required biomarkers, the participant may simultaneously sign the pre-screening and main consent forms, enter main screening and submit the tissue sample prior to start of treatment (Section 8.1).
*** Mandatory where sample is available and to be requested from another institution. Not required if tumor tissue block was submitted during pre-screening/screening for PD-L1, KRAS G12C and/or STK11 assessment or if optional, newly obtained biopsy is provided at C1D1.

Biomarker assessments for molecular pre-screening

A tumor sample (archival tumor block or slides, as detailed in Table 8-9) and a blood sample are required from all participants as part of the molecular pre-screening assessments of this trial. The samples will be used for centralized eligibility assessment for PD-L1 expression, KRAS G12C and STK11 (cohort B only) mutation status, when local test results confirming eligibility are not available or for retrospective confirmation of biomarker status where local

test results are available for any of the biomarkers (as described in Section 8.1). For participants in China only: PD-L1 expression, KRAS G12C status and STK11 mutation status (STK11 mutation for cohort B only) must be determined by local assessment. Tumor sample material and blood may also be used to support diagnostic test development. If available, a copy of the corresponding de-identified pathology report should be submitted with archival tumor samples. Tumor samples must contain at least 20% tumor content. Samples obtained from bone metastases and cytology samples are not acceptable.

Exploratory biomarker assessments in tumor

At C1D1, all participants are required to submit a tumor sample (where available) as an archival tissue block or slides or may optionally provide a newly acquired core or excisional formalin-fixed biopsy sample. The sample is not required to be submitted if tumor tissue block was submitted during pre-screening/screening for PD-L1, KRAS G12C and/or STK11 assessment. All participants will also be asked to optionally provide newly acquired, core or excisional, formalin-fixed biopsy samples at C1D1, C1D15 collected 4 to 8 hours post-dose and at first disease progression, prior to the initiation of any new anti-cancer therapies. Participants must sign the relevant section of the ICF to consent to the optional biopsy collection(s).

Tumor tissue material collected at pre-screening, C1D1 (if a tissue block was not submitted at pre-screening or optionally from a newly obtained biopsy) and optionally at C1D1, C1D15 and disease progression will be used to support exploratory biomarker assessments including CCI [redacted]. Analysis methods may include CCI, CCI CCI and CCI.

CCI [redacted] including but not limited to CCI and CCI may be investigated in baseline and on-treatment samples (if available) to assess quantitative changes as well as the CCI [redacted] to the treatment, as measured by CCI, CCI by CCI or using additional techniques deemed suitable. The biopsy at disease progression will be used to unveil potential CCI [redacted], or to highlight CCI [redacted]

Biomarker assessments in blood

Blood will be collected as detailed in Table 8-9 to allow for sequencing of plasma cell CCI [redacted] to support diagnostic test development, and/or for CCI [redacted]

Baseline levels and longitudinal changes over time of CCI [redacted] and selected CCI [redacted] may be assessed with respect to clinical endpoints.

All blood samples collected on the study for biomarker analysis may be interchangeably used for analyzing CCI [redacted] and other circulating markers of interest to address scientific questions related to KRAS inhibition, lung cancer, treatment response or clinical outcome.

A targeted CCI [redacted] may be used to assess CCI [redacted] associated with NSCLC and the CCI [redacted] to understand CCI [redacted]. When there is a matching tissue sample available, correlation of markers with tumor tissue will be assessed. Additional CCI [redacted] and CCI [redacted] associated with NSCLC and CCI [redacted] may also be analyzed.

8.9.1 Use of residual biological samples

Optional additional biomarker studies

If the participant agrees (for participants enrolled in China, conditional upon approval from local authorities [including but not limited to HGRAC]), the biological samples (tumor, blood, plasma, and serum) may be kept for up to 15 years to be used for additional studies related to JDQ443 or cancer, including research to help develop ways to detect, monitor or treat cancer. Soluble/protein markers may also be measured on those samples to better understand the disease and response to treatment. A decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

8.10 CCI [redacted] assessments

CCI [redacted] is not evaluated in this study.

9 Statistical considerations

The efficacy and safety analyses will be performed separately for each of the two cohorts and the STK11-mutated participants pooled from the two cohorts. The primary analysis of the primary and key secondary endpoint will be conducted on all participant data when participants in the respective cohort who are still receiving study treatment will have completed at least 4 tumor assessments (approximately 24 weeks).

Any additional data for participants continuing to receive study treatment past the data cut-off date for the primary analysis in each of the groups will be reported at completion of the study in a final CSR.

9.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned and who received at least one dose of study treatment.

The Safety Set includes all participants who received at least one dose of study treatment.

The FAS and Safety Set in this study are identical.

The Pharmacokinetic Analysis Set (PAS) includes all participants who received at least one planned dose of study treatment and provide an evaluable pharmacokinetic concentration.

Criteria described below need to be considered for a concentration to be evaluable:

- Participant did not vomit within 4 hours after dosing of JDQ443
- For all pre-dose samples, PK draw occurred before the next dose intake
- For post-dose PK samples, PK draw with concentration following planned dose
- Any PK blood samples with missing collection date or time, or missing associated study treatment dosing date or time will be excluded.

The Full Pharmacokinetic Analysis Set (FPAS) includes PAS participants with intensive PK collection schedule who provide an evaluable PK profile. A profile is considered evaluable if the conditions listed for the PK Analysis Set (Section 9.4.3) and the following conditions are met:

- Participant receives planned dose
- Participant provides at least one valid primary PK parameter

Further details will be included in the Statistical Analysis Plan (SAP).

9.2 Statistical analyses

9.2.1 General considerations

The efficacy analyses will be performed separately for each of the two cohorts. An additional group including all participants whose tumors harbor an STK11 mutation will be formed by pooling participants from cohorts A and B. Unless otherwise specified, efficacy analyses conducted for the 2 cohorts will also be performed for the pooled group. The description "by cohort" or "for each cohort" will include these analyses.

The criteria for the targeted ORR and the respective 95% confidence interval assumptions adopted for both cohorts, i.e., for both the primary and the key secondary endpoint, were based on the assumption that JDQ443 will present a similar level of antitumor activity than the one observed in previous studies with KRAS G12C inhibitors in patients with KRAS G12C-mutated advanced NSCLC (Riely et 2021, Skoulidis et al 2021). For cohort B, the criterion chosen for success (ORR of 40% and the CI lower limit of 20%) was slightly more conservative than for cohort A. Due to the sample size of cohort B, a difference in responders of a single participant may generate a high impact in the efficacy assessments.

9.2.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by cohort for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by cohort.

9.2.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. The exposure related analyses will be presented by cohort.

The duration of exposure to JDQ443 in weeks as well as the dose intensity and the relative dose intensity will be summarized by means of descriptive statistics. The number of participants with dose adjustments (reductions, interruption, or permanent discontinuation) and the reasons will be summarized. All dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized by cohort.

9.3 Primary endpoint(s)/estimand(s) analysis

The primary objective of the study is to assess the antitumor activity of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1%, regardless of STK11 mutation status (cohort A).

9.3.1 Definition of primary endpoint(s)

The primary endpoint of the study is ORR, defined as the proportion of participants with a confirmed CR/PR as BOR. BOR is defined as the best response recorded from the start of the treatment until disease progression per RECIST 1.1 by BIRC. CR and PR must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response were first met. Responses documented after the use of any new anti-neoplastic therapy will be considered as non-response.

9.3.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be performed on the FAS. The primary efficacy endpoint ORR will be estimated and the exact 95% confidence interval (CI) (Clopper and Pearson 1934) provided.

Treatment with JDQ443 will be considered to have clinically relevant efficacy if an ORR of CCI (per RECIST 1.1 by BIRC assessment) is observed with the lower bound of the 95% confidence interval CCI. The following statistical hypotheses will be tested:

H_0: ORR CCI vs. H_1 ORR $\geq$ 35%.

The tests will be performed based on the exact confidence interval for ORR using a one-sided α=0.025 level. The null hypothesis will be rejected if the lower bound of the two-sided 95% exact CI is $\geq$ 35%.

An interim analysis for futility will be performed to assess ORR in approximately the first 30 evaluable participants. Evaluable participants are defined as enrolled participants who have been followed for at least two tumor assessments or have discontinued the study earlier (see Section 9.8).

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

The primary analysis will account for different intercurrent events as explained in the following:

1. Discontinuation of study treatment: Tumor assessment data collected after discontinuation of study treatment for any reason will be included to derive BOR (treatment policy strategy).
2. Start of a new anti-neoplastic therapy: If any new anti-neoplastic therapy is initiated, responses documented after the use of new anti-neoplastic therapy will be considered as non-response (composite strategy).
3. Any public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster: Tumor assessment data collected irrespective of such unforeseen events will be considered for the BOR (treatment policy strategy).

9.3.4 Handling of missing values not related to intercurrent event

Confirmed PR or CR reported prior to any additional anticancer therapy will be considered as responses in the calculation of the ORR irrespective of the number of missed assessments before response.

Participants with a BOR of 'Not evaluable' per RECIST 1.1 will be considered as non-responders when estimating ORR. Participants who have disease progression and continue to receive study treatment after progression per RECIST 1.1 by BIRC will qualify for PD at the time of progression and will be counted as PD in the derivation of BOR.

9.3.5 Multiplicity adjustment (if applicable)

As the 2 cohorts represent different patient populations, a multiplicity adjustment for the analysis of the primary and first key secondary endpoints is not applicable. For the analysis of the other key secondary endpoints there is also no multiplicity adjustment planned.

9.3.6 Sensitivity analyses

Not applicable.

9.3.7 Supplementary analysis

A supplementary estimand is defined by the same target population, treatment of interest, intercurrent events, and summary measure as for the primary estimand. Differently from the primary estimand, the primary variable is the BOR per RECIST 1.1 assessed by the Investigator (local assessment), with responses documented after the use of any new anti-neoplastic therapy considered as non-response.

The method of analysis, handling of intercurrent events, and missing data will be the same as described in Section 9.3.2, Section 9.3.3, and Section 9.3.4.

9.4 Secondary endpoint(s)/estimand(s) analysis

The secondary objectives in this study are to assess the antitumor activity of JDQ443 single-agent as first-line treatment for participants with locally advanced or metastatic NSCLC whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1% and an STK11 co-mutation (cohort B), and to evaluate the duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), time to response (TTR), overall survival (OS), pharmacokinetics, safety, as well as patient-reported symptoms, impacts, functioning and tolerability with patient-outcomes (PRO).

ORR per RECIST 1.1 by BIRC for cohort B and DOR per RECIST 1.1 by BIRC in both cohorts are identified as the key secondary endpoints. No multiplicity adjustment is foreseen in the analysis of the key secondary or other secondary endpoints.

9.4.1 Efficacy and/or pharmacodynamic endpoint(s)

The secondary efficacy endpoints will be assessed using the FAS.

9.4.1.1 Key secondary endpoints

For the key secondary endpoint, ORR per RECIST 1.1 by BIRC in cohort B, the same definition as in Section 9.3.1 applies.

Treatment with JDQ443 will be considered to have clinically relevant efficacy in cohort B if an ORR of ≥ 40% is observed with the lower bound of the 95% confidence interval ≥ 20%. The following statistical hypotheses will be tested:

H_0: ORR < 20% vs. H_1: ORR ≥ 20%.

The test will be performed based on the exact confidence interval for ORR using a one-sided α=0.025 level. The null hypothesis will be rejected if the lower bound of the two-sided 95% exact CI is ≥ 20%. The ORR and its 95% confidence interval will be presented.

An interim analysis for futility will be performed to assess the ORR in approximately the first CCI participants. Evaluable participants are defined as enrolled participants who have been followed for at least two tumor assessments or have discontinued the study earlier (see Section 9.8).

As a supportive analysis, ORR per RECIST 1.1 as assessed by local review along with 95% confidence intervals will be presented for both cohort A and cohort B.

DOR only applies to participants whose best overall response is CR or PR according to RECIST 1.1 by BIRC. The start date is the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to any cause. Participants continuing without progression or death will be censored at the date of their last adequate tumor assessment.

DOR will be listed and summarized by cohort for all participants with confirmed BOR of CR or PR. The DOR distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each cohort.

As a supportive analysis, DOR per RECIST 1.1 as assessed by local review, will be summarized by cohort.

9.4.1.2 Other secondary efficacy endpoints

DCR is defined as the proportion of participants with a BOR of confirmed CR, PR and stable disease (SD) according to RECIST 1.1 (see Appendix 8 Section 10.8). DCR will be assessed by BIRC as well as by local review. DCR and the corresponding 95% confidence intervals based on the exact binomial distribution (Clopper and Pearson 1934) will be presented.

PFS is defined as the time from the date of first dose of study treatment to the date of the first documented progression or death due to any cause. PFS will be assessed by BIRC as well as by local review according to RECIST 1.1 (see Section 10.8 for further details). PFS will be censored if no PFS event is observed before the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy is started. The censoring date will be the date of the last adequate tumor assessment prior to cut-off/start of new anti-neoplastic therapy. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each cohort.

Time to response (TTR) is defined as the time from the date of first dose of study treatment to the first documented response of either CR or PR, which must be subsequently confirmed (although date of initial response is used, not date of confirmation). CR and PR are based on tumor response data by BIRC as well as per local review and according to RECIST 1.1 (see Section 10.8 for details). All participants in the FAS will be included in TTR calculations. Participants without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e., LPLV−FPFV) for participants with a PFS event (i.e., disease progression or death due to any cause), or at the date of the last adequate tumor assessment for participants without a PFS event. TTR will be listed and summarized by cohort. The TTR distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each cohort.

OS is defined as the time from the date of first dose of study treatment to the date of death due to any cause. If a participant is not known to have died, then OS will be censored at the latest date the participant was known to be alive (on or before the cut-off date). The OS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each cohort.

9.4.2 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by cohort.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g., change from

baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before first dose of the study treatment
2. On-treatment period: from day of first dose of the study treatment to 30 days after last dose of the study treatment
3. Post-treatment period: starting at day 31 after last dose of the study treatment.

9.4.2.1 Adverse events

All information obtained on AEs will be displayed by cohort and participant.

The number (and percentage) of participants with treatment emergent AEs (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- By treatment, primary system organ class and preferred term
- By treatment, primary system organ class, preferred term and maximum severity

Separate summaries will be provided for study medication related AEs, deaths, SAEs, other significant AEs leading to discontinuation, and AEs leading to dose adjustment.

The number (and proportion) of participants with adverse events of special interest (AESI) will be summarized by cohort. AESIs will be defined based on the case retrieval strategy (CRS) available at the time of the analysis.

A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

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

All AEs, deaths and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

9.4.2.2 Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests where grades are not defined by CTCAE version 5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

All laboratory data will be summarized by cohort. The following summaries/listings will be generated separately for hematology and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE version 5.0

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline
- Shift tables using CTCAE version 5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 5.0,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

In addition to the above-mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots may be specified in the analysis plan.

9.4.2.3 Vital signs

Vital signs parameter measured include blood pressure (supine position preferred when ECG is collected), pulse measurement, respiratory rate and body temperature.

Data on vital signs will be tabulated and listed by cohort, visit/time, notable values will be flagged. Summary statistics will be provided by cohort.

9.4.2.4 12-lead ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted centrally.

Notable ECG abnormalities will be summarized. In addition, a listing of these participants will be produced by cohort.

9.4.3 Pharmacokinetics

The FAS will be used to list individual concentration data. The PAS will be used for summary statistics of JDQ443 concentration data and the FPAS for all PK analyses (non-compartmental and pharmacometric) including summary statistics of PK parameters.

JDQ443 concentration data will be listed by cohort, participant, and visit/sampling time point. Descriptive summary statistics will be provided by cohort and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics of concentration data will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A graphical presentation will be provided on mean concentration at each scheduled time point when the full PK profile is available.

Individual and mean PK parameters such as listed in Table 9-1 will be derived using non-compartmental analysis using Phoenix WinNonlin (Version 5.0 or higher) and reported, if feasible.

Descriptive summary statistics of PK parameters will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is T_{max} where median, minimum, and maximum will be presented.

Table 9-1 JDQ443 plasma pharmacokinetic parameters - non-compartmental analysis

$AUC_{last,ss}$	The AUC from time zero to the last measurable concentration sampling time (t_{lastss}) at steady-state (mass × time × volume^{-1})
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount × time × volume^{-1})
$C_{max,ss}$	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentrations after single dose administration (mass × volume^{-1})
$T_{max,ss}$	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration at stead-state (time)
$C_{min,ss}$	Observed concentration at the end of a dosing interval (taken directly before next administration) at steady-state
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (time^{-1}) may also be used for terminal elimination rate constant at steady-state (time^{-1})
$T_{1/2,ss}$	The elimination half-life associated with the terminal slope (λ_z) of a semi logarithmic concentration-time curve at steady-state (time).
CL/F	The total body clearance of drug from the plasma (volume × time^{-1})
V_z/F	The apparent volume of distribution during terminal phase (associated with λ_z) (volume)

9.4.4 Patient-reported outcomes

The following patient-reported outcomes (PRO) questionnaires will be assessed: the NSCLC-SAQ, EORTC QLQ-C30, the FACT-GP5, PRO-CTCAE and the EQ-5D-5L. Of these the NSCLC-SAQ, EORTC QLQ-C30, and FACT-GP5 will be analyzed by cohort (A and B) to assess the secondary objectives. The other questionnaires may be evaluated in exploratory analyses.

The FAS will be used for analyzing PRO data.

Scoring of PRO data and methods for handling of missing items or missing assessments will be according to the scoring manual and user guide for each respective participant questionnaire (Aaronson et al 1993, Fayers et al 2001, McCarrier et al 2016). No imputation procedures will be applied for missing items or missing assessments.

Time to definitive deterioration in the NSCLC-SAQ total score is the primary PRO variable of interest. Time to definitive deterioration (TTDD) in physical functioning (PF)of the QLQ-C30 is the secondary PRO variable of interest.

The time to definitive 10-point deterioration for SAQ total score (TS) or C30 PF, respectively, is defined as the time from the date of enrollment to the date of meaningful worsening. For the TS it is defined as at least 1-point absolute increase in score from baseline (worsening), and for PF it is defined as at least 10-point absolute decrease in score from baseline (worsening) , with no later improvement above these thresholds during the course of the treatment or until death

due to any cause (within 3 weeks of the last assessment). If a participant has not had an event, time to definitive deterioration will be censored at the date of the last adequate PRO assessment. Only assessments collected while the participant is on treatment and at the end of treatment visit will be included in the PRO TTDD. Participants with no baseline data or no post-baseline data will be censored at baseline.

The distribution of time to definitive deterioration will be summarized using the Kaplan-Meier method, and the Kaplan-Meier curves, medians, and two-sided 95% confidence intervals of the medians will be presented. Additionally, time to definitive deterioration with different cut-off definitions for deterioration may be specified in the SAP as deemed appropriate.

Descriptive statistics will be used to summarize the scores, as well as change from baseline, of the EORTC QLQ-C30, EQ-5D-5L,NSCLC-SAQ and PGIS-NSCLC at each scheduled assessment and to EOT. Additionally, change from baseline scores will assess SAQ total score, pain and fatigue domains, and cough, dyspnea and appetite loss items; C30 GHS/QoL and functional domains as well as symptom items/domains and financial problems item. Participants with an evaluable baseline score and at least one evaluable post-baseline score during the on-treatment period will be included in the change from baseline analyses.

The number of participants completing each PRO and the number of missing or incomplete assessments will be summarized by cohort for each scheduled assessment timepoint. No formal statistical tests will be performed for PRO data and hence no multiplicity adjustment will be applied.

9.5 Exploratory endpoint(s)/estimand(s) analysis

Further details for the analysis of exploratory endpoints might be provided in the statistical analysis plan.

9.5.1 Biomarkers

The statistical goals of exploratory biomarker analysis should be considered as promoting the generation of new scientific hypotheses and are exploratory in nature.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons (e.g., issues related to the quality and/or quantity of the samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

9.5.1.1 Outline of the data analysis

The proposed data analysis will be aligned with the exploratory biomarker objectives of the protocol:

- To assess CCI [redacted]
- To assess CCI [redacted]

- To explore the CCI [redacted]
- To assess the relationship CCI [redacted]

9.5.1.2 Data analysis principles

The FAS will be used for all biomarker analyses unless otherwise specified.

Depending on the endpoint of interest, graphical displays such as box plots or strip plots may be used to assess the relationship of different biomarkers with clinical benefit. These may be separated by cohort and include either baseline or change from baseline values, where applicable.

For continuous markers, baseline and change from baseline (absolute change, percent change and fold change) at each time point will be summarized in tables that include sample size, mean, standard deviation, CV%, median, minimum and maximum. For fold change from baseline, geometric mean and geometric CV% will also be included. For categorical markers such as mutation status, 2×2 contingency tables may be used to assess the relationship with clinical benefit and/or Kaplan-Meier curves may be generated given the number of events warrant such an assessment.

If additional analyses are needed to be performed after the completion of the end-of-study clinical study report (CSR), they will be documented in separate reports. The data analysis will be described in an addendum of the statistical analysis plan (SAP) or in a stand-alone analysis plan document, as appropriate.

9.5.2 Pharmacokinetics

Pharmacokinetic data from this study will be analyzed using population PK approach, which may include exploring the effect of covariates on PK, if data allow. The PK data from this study may be combined with similar data from other studies and explored using population PK. Exploratory analyses may also be conducted to identify possible relationships of JDQ443 exposure (e.g., Cmax, Cmin or AUC) with PD markers, clinical efficacy (ORR, PFS, and OS) or safety variables as appropriate. The results of such exploratory analyses will be reported separately from the CSR.

9.6 (Other) Safety analyses

Not applicable

9.7 Other analyses

Not applicable

9.8 Interim analysis

The planned interim analyses will be performed separately for each of the two cohorts. In case the interim analysis (IA) of the two cohorts happens at a similar time, the IA will be reported together.

9.8.1 Primary endpoint: ORR in cohort A

One IA is planned for cohort A based on approximately the first 30 evaluable participants. Evaluable participants are defined as enrolled participants who have been followed for at least two tumor assessments or have discontinued the study earlier. The primary intent of the interim analysis is to stop the cohort early for lack of efficacy (futility).

The decision whether to continue or stop enrollment and/or treatment will be based on the predictive probability of success (PPoS). PPoS is the predictive probability of a positive conclusion of the study (regarding cohort A) if it continued beyond the interim analysis (i.e., until the final analysis), given the interim observed data (x) and successes among n participants.

PPoS = Prob[Final observed ORR ≥ CCI% | x, n]

A minimally informative Beta distribution prior (Neuenschwander et al 2008) with prior mean equal to CCI% will be used, i.e., the prior distribution will be Beta (CCI for the PPoS calculations at the interim analysis.

The cohort will be stopped for futility at the interim analysis if the observed ORR is ≤ CCI% corresponding to 9 or less responders (at least CCI responders out of 30 participants are required for the study to proceed). If the futility criterion is met, the predictive probability of observing a success in the future based on the existing data will be < CCI%.

All evaluable participants in cohort A at the time of the data cut-off for the interim analysis will be used.

If futility is concluded, the enrollment of participants in the cohort will be stopped. The enrollment in cohort B will continue, if applicable.

Table 9-2 provides the PPoS at the primary analysis based on different numbers of responders observed at the interim analysis. For CCI responders, PPoS exceeds CCI% and the cohort will continue after the interim analysis.

Table 9-2 PPoS at the primary analysis based on various numbers of responders observed at the IA

Responders at IA out of 30 evaluable participants	Predictive probability of success (%)
5	CCI
6	CCI
7	CCI
8	CCI
9	CCI
10	CCI
11	CCI
12	CCI

9.8.2 Key secondary endpoint: ORR in cohort B

One interim analysis is planned for cohort B based on approximately the first CCI evaluable participants. Evaluable participants are defined as enrolled participants who have been followed for at least two tumor assessments or have discontinued the study earlier. The primary intent of the interim analysis is to stop the cohort early for lack of efficacy (futility).

The decision whether to continue or stop enrollment and/or treatment will be based on the PPoS.

PPoS = Prob[Final observed ORR ≥ [redacted]% | x, n]

A minimally informative Beta distribution prior (Neuenschwander et al 2008) with prior mean equal to [redacted]% will be used, i.e., the prior distribution will be Beta([redacted] for the PpoS calculations at the interim analysis.

The cohort will be stopped for futility at the interim analysis if the observed ORR is ≤ [redacted]% corresponding to [redacted] or less responders (at least [redacted] responders out of [redacted] participants are required for the cohort to proceed). If the futility criterion is met, the predictive probability of observing a success in the future based on the existing data will be <[redacted]%.

All evaluable participants in the cohort at the time of the data cut-off for the interim analysis will be used.

If futility is concluded, the enrollment of participants in the cohort will be stopped. The enrollment in cohort A will continue, if applicable.

Table 9-3 provides the PPoS at the primary analysis based on different numbers of responders observed at the interim analysis. For [redacted] or more responders, PPoS exceeds [redacted]% and the cohort will continue after the interim analysis.

Table 9-3 PPoS at the final analysis based on various numbers of responders observed

Responders at IA out of [redacted] participants	Predictive probability of success (%)
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]

9.9 Sample size determination

A total of 120 participants will be enrolled in 2 separate cohorts that will recruit in parallel: 90 in cohort A and 30 in cohort B, if none of the cohorts is stopped for futility at the time of the corresponding interim analysis.

An additional group including all participants whose tumors harbor an STK11 mutation will be formed by pooling participants from cohorts A and B. Around 30 of these participants are anticipated in cohort B and another ~30 STK11 mutated participants are expected from cohort A based on the prevalence of STK11 mutation among patients with KRAS G12C-mutated advanced NSCLC in prior studies, hence the STK11 mutated group should have approximately 60 participants (Ricciuti et al 2021).

9.9.1 Primary endpoint(s)

The calculation of sample size and operating characteristics for the analysis of the primary endpoint, ORR estimate and confidence interval, are based on the model and assumptions in Section 9.3.2.

The exact 95% CIs for various sample sizes and potential observed ORRs are shown in Table 9-4.

Table 9-4 Exact binomial 95 percent confidence intervals for various sample sizes and observed ORRs (cohort A)

Sample size (N)	Number of responders	Observed ORR (%)	95% exact CI (%)
CCI			

The operating characteristics (for 90 participants) are shown in Table 9-5. The table presents the probability of stopping at the interim, the probability for a positive conclusion (i.e., not stopped at IA for futility and success criteria met at final analysis), and a negative conclusion (i.e., not stopped at IA for futility but success criteria not met at final analysis) under different underlying true ORR.

Table 9-5 Operating Characteristics (cohort A)

True ORR (%)	Prob. to stop at IA* (%)	Prob. of success at final analysis (%)	Prob. of failure at final analysis (%)
CCI			

*Assuming IA at 30evaluable participants

The operating characteristics at this sample size have around CCI probability of stopping the trial for futility when the true ORR is CCI or less. Also, when the true ORR is CCI, the probability of a positive conclusion at the final analysis with 90 participants is around CCI. For a true ORR of 50% or higher, the probability of a positive conclusion at the final analysis is CCI

The calculations were made using the software R.

9.9.2 Secondary endpoint(s)

The calculation of sample size and operating characteristics for the analysis of the key secondary endpoint, cohort B ORR estimate and confidence interval, are based on the model and assumptions in Section 9.4.1.1.

The exact 95% CIs for various sample sizes and observed ORRs are shown in Table 9-6 .

Table 9-6 Exact binomial 95 percent confidence intervals for various sample sizes and observed ORRs (cohort B)

Sample size (N)	Number of responders	Observed ORR (%)	95% exact CI (%)
CCI			

The operating characteristics (for 30 participants) are shown in Table 9-7. The table presents the probability of stopping at the interim, the probability for a positive conclusion (i.e., not stopped at IA for futility and success criteria met at final analysis), and a negative conclusion (i.e., not stopped at IA for futility but success criteria not met at final analysis) under different underlying true ORR.

Table 9-7 Operating characteristics (cohort B)

True ORR	Prob. to stop at IA* (%)	Prob. of success at final analysis (%)	Prob. of failure at final analysis (%)
CCI			

*Assuming IA at CCI participants

The operating characteristics at this sample size have around CCI probability of stopping the trial for futility when the true ORR is CCI or less. Also, when the true ORR is CCI, the probability of a positive conclusion at the final analysis with 30 participants is circa CCI. If the true ORR is 50% or higher, the probability of a positive conclusion at the final analysis is CCI

The calculations were made using the software R.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

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

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

The protocol, protocol amendments, ICF, Investigator's Brochure, [IDFU], and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable

local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

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

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

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

A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

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

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional 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 additional research. Participants who decline to participate in this optional additional research will document this.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate,

for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Molecular pre-screening consent
- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - A subsection that requires a separate signature for the 'Optional Collection of Tumor Biopsy'
  - Optional consent for activities that may be done outside of the study site
- As applicable, Treatment Beyond Progression Consent
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Patient information sheet for female partners of any male participants who took study treatment

Declining to participate in these optional assessments will in no way affect the participant's ability to join the main research study.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

10.1.3 Data protection

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

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

10.1.4.1 Steering Committee

The Steering Committee (SC) will be established comprising Investigators participating in the trial or experts in the disease area and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the SC will be defined in the SC charter.

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan, contracts.

Records and documents, including signed ICFs, pertaining to the conduct of this study 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 Novartis. No records may be transferred to another location or party without written notification to Novartis.

Efforts should be made to collect all data that are relevant to support a statistical analysis aligned with the estimands of interest. If the estimands that are required to support regulatory decision making do not require the collection of the variable after an intercurrent event, then the benefits of collecting such data for other estimands should be weighed against any complications and potential drawbacks of the collection.

10.1.5.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on eCRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.1.5.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of pre-screenings, screenings, enrollments, screen failures and study completion, and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

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

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

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in relevant monitoring guidances.

The Investigator must maintain accurate documentation (source data) that supports the information entered into the eCRF. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during scheduled and ad hoc on-site or remote monitoring visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis /CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT or CTIS public website. In addition, after study completion (Section 4.7) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g., Clinicaltrials.gov, EudraCT or CTIS public website etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ANCOVA	Analysis of covariance
ASMA	Anti-smooth muscle antibody
AST	Aspartate Aminotransferase
b.i.d.	bis in die/twice a day
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
COA	Clinical Outcome Assessment
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria Adverse Event
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DIN	Drug Inducted Nephrotoxicity
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer
ERCP	Endoscopic retrograde cholangiopancreatography
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FDA	Food and Drug Administration
FIH	First in Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase

GLDH	Glutamate Dehydrogenase
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HGRAC	Human Genetic Resource Administration Of China
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MTD	Maximum Tolerated Dose
p.o.	oral(ly)
PD	Pharmacodynamic(s) / Progressive disease
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PS&PV	Patient safety and pharmacovigilance
PT	prothrombin time
QD	Once a day
QoL	Quality of life
QTcF	QT interval corrected by Fridericia’s formula
R Value	ALT/ALP x ULN
RAP	The Report and Analysis Plan
RD	Recommended Dose
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation / stable disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

ULN	upper limit of normal
UTI	Urinary Tract Infection
WHO	World Health Organization
WoC	Withdrawal of Consent

10.2.2 Definitions

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.

Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

Not Applicable

10.4 Appendix 4: Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis

- Thank You letter
- Plain language trial summary - after CSR publication

10.5 Appendix 5: Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed

Please refer to Table 10-1 in Section 10.5 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 6-3 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 10-1 and Table 10-2. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
  - These investigations can include based on Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

Table 10-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 x ULN • ALP > 2 x ULN (in the absence of known bone pathology) • Total bilirubin > 3 x ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 x ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 x ULN and Total bilirubin > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 x ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3 x baseline or > 300 U/L (whichever occurs first)

Table 10-2 Follow-up requirements for liver laboratory triggers - ALT, AST, bilirubin

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			

ALT	TBL	Liver Symptoms	Action
If normal at baseline: ALT > 3 x ULN **If elevated at baseline**: ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	· **No change to study treatment** · Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. · Follow-up for symptoms.
If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline**: ALT > 3 x baseline or > 300 U/L (whichever occurs first) for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	· **Interrupt study treatment** · Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. · Follow-up for symptoms. · Initiate close monitoring and workup for competing etiologies. · Study treatment can be restarted only if another etiology is identified and liver enzymes return to baseline.
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN **If elevated at baseline**: ALT > 2 x baseline or > 300 U/L (whichever occurs first)	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If normal at baseline: ALT > 3 x ULN **If elevated at baseline**: ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 10-3 Follow-up requirements for liver laboratory triggers - isolated hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate eCRF	resolution (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate eCRF	Investigator discretion

10.6 Appendix 6: Renal safety monitoring

Upon diagnosis and confirmation of a renal event, some general procedures and some event specific activities (Table 10-4 and Table 10-5) are indicated depending on the severity of the event and the clinical status of the subject. Note, all events should be documented in the CRF

Table 10-4 Specific renal alert criteria and actions

Renal events	Actions
Creatinine clearance decrease 25 - 49%	• Consider causes and possible interventions • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI (acute kidney injury), etc.
Creatinine clearance decrease ≥ 50 % [+] OR if <18 years old, Creatinine clearance < 35 mL/min/1.73 m^2	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider referral to nephrologist for diagnosis and management • Consider patient hospitalization and specialized treatment • Confirm presence of true proteinuria by quantification: protein:creatinine on first morning void
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Creatinine (Cr)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider referral to a nephrologist
New onset hematuria ≥ 3+ on urine dipstick	• Obtain urine microscopy to distinguish hemoglobinuria or myoglobinuria from hematuria • Assess serum creatinine (sCr) • Exclude infection, trauma, calculi, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+]Corresponds to Kidney Disease Improving Global Outcomes (KDIGO) criteria for Acute Kidney Injury

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, cardiac murmur, back or abdominal pain, hepatomegaly, dysuria or hematuria, dependent or periorbital edema
- Changes in body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

- Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG to potentially identify project wide patterns of nephrotoxicity).

Table 10-5 Renal event follow-up

FOLLOW-UP OF RENAL EVENTS
• Monitor patient regularly ((frequency dependent on clinical course and consultant advisement) until –
• Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or
• Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.
• Analysis of urine markers in samples collected over the course of the drug induced nephrotoxicity (DIN) event

10.7 Appendix 7: Drugs that are prohibited or to be used with caution while on JDQ443 treatment

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient is permitted except when specifically prohibited.

Drugs which are strong CYP3A inducers are prohibited (Table 10-6). If a drug listed as to be used with caution is also listed under the prohibited drug list then use of that drug is prohibited.

Table 10-6 Drugs to be prohibited while on treatment with JDQ443

Category	Drug Name
Strong CYP3A inducers	apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, mitotane, lumacaftor, phenobarbital, phenytoin, rifampicin, rifapentine, St. John's wort (*Hypericum perforatum*)[1]

The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (Jan 2021): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies".
This is not a comprehensive list. Please contact the medical monitor with any questions.
[1] Herbal product

Table 10-7 Drugs to be used with caution while on treatment with JDQ443

Category	Drug Name
Strong CYP3A inhibitors	boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir[4], elvitegravir/ritonavir[4], grapefruit juice[3] , idelalisib, indinavir, indinavir/ritonavir[4], itraconazole, josamycin, ketoconazole, lopinavir/ritonavir[4], mibefradil, mifepristone, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[4], posaconazole, ribociclib, ritonavir, saquinavir, saquinavir/ritonavir[4], telaprevir, telithromycin, tipranavir/ritonavir[4], troleandomycin, tucatinib, voriconazole
CYP2B6 sensitive substrates or substrates with NTI	ifosfamide, tamoxifen, thiotepa
CYP2C8 sensitive substrates or substrates with NTI	carbamazepine, dabrafenib, erlotinib, paclitaxel, dasabuvir, repaglinide, daprodustat
CYP2C9 sensitive substrates or substrates with NTI	(S)-warfarin, celecoxib, erdafitinib, phenytoin, quinidine, siponimod, tamoxifen, benzbromarone, glimepiride, glipizide, ibuprofen, lornoxicam, meloxicam, piroxicam, tolbutamide
CYP2C19 sensitive substrates or substrates with NTI	(S)-mephenytoin, clobazam, (R)-lansoprazole (dexlansoprazole), diazepam, gliclazide, (S)-lansoprazole, (R)-mephobarbital, (R)-omeprazole, omeprazole, pantoprazole, proguanil, rabeprazole, tilidine, amitriptyline, clomipramine, imipramine, R)-(-)-hexobarbital, voriconazole
CYP3A sensitive substrates or substrates with NTI	abemaciclib, acalabrutinib, alectinib amiodarone, amitriptyline, astemizole, axitinib, baricitinib, bosutinib, brigatinib, cabazitaxel, cabozantinib, carbamazepine, ceritinib, clomipramine, cobimetinib, conivaptan, copanlisib, crizotinib, cyclosporine, dabrafenib, dasatinib, dihydroergotamine, docetaxel, dronedarone, entrectinib, erdafitinib, ergotamine, everolimus, imipramine, ivosidenib, ixazomib, lomitapide, midostaurin, neratinib, nilotinib, panobinostat, pexidartinib, pimozide, ponatinib, quinidine, regorafenib, romidepsin, sirolimus, sonidegib, sorafenib, sunitinib, tacrolimus, tamoxifen, temsirolimus, tolvaptan, trabectedin, venetoclax, vinblastine, zanubrutinib abemaciclib, acalabrutinib, alisporivir, almorexant, alfentanil, alpha-dihydroergocryptine, aplaviroc, aprepitant, asunaprevir, atazanavir, atorvastatin, avanafil, avapritinib, blonanserin, bosutinib, brecanavir, brigatinib, brotizolam, budesonide, buspirone, cabazitaxel, carbamazepine, capravirine,

Category	Drug Name
	casopitant, cobicistat, cobimetinib, conivaptan, cyclosporine, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eliglustat, elvitegravir, entrectinib, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, indinavir, isavuconazole, itacitinib, ivabradine, ivacaftor, levomethadyl (LAAM), lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, morphothiadin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, sirolimus, tacrolimus, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ubrogepant, ulipristal, vardenafil, venetoclax, vicriviroc, vilaprisan, voclosporin, voriconazole, zanubrutinib
OATP1B1/3 Substrates or substrate with NTI	aliskiren, ambrisentan, anacetrapib, atenolol, asunaprevir, atorvastatin, bosentan, bromocriptine, caspofungin, celiprolol, danoprevir, digoxin, docetaxel, eliglustat, empagliflozin, ezetimibe, fimasartan, fexofenadine, fluvastatin, glyburide, maraviroc, methotrexate, montelukast, nateglinide, olmesartan, revefenacin, paclitaxel, pitavastatin, pravastatin, repaglinide, rifampicin, rosuvastatin, saquinavir, simvastatin, telmisartan, tezacaftor, thyroxine, ticlopidine, valsartan
P-gp Substrates P-gp substrates with NTI[1]	cyclosporine, digoxin, docetaxel, doxorubicin, eribulin, everolimus, fentanyl, idelalisib, ivosidenib, paclitaxel, pazopanib, phenytoin, quinidine, sirolimus, sorafenib, tacrolimus, talazoparib, tolvaptan, topotecan, vincristine
P-gp substrates with ≥2X AUC change[2]	aliskiren, ambrisentan, atorvastatin, azithromycin, berotlarastat, colchicine, dabigatran, digoxin, docetaxel, domperidone, doxorubicin, elexacaftor, fedratinib, fentanyl, fexofenadine, lapatinib, lefamulin, linezolid, loperamide, maraviroc, nadolol, nevirapine, paclitaxel, proguanil, quinidine, ranolazine, relugolix, ritonavir, saquinavir, simvastatin, sirolimus, sofosbuvir, tacrolimus, tezacaftor, ticagrelor, topotecan
Herbal Medications	Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh, ginseng, etc.

[1] These drugs have both a narrow therapeutic index and an *in vivo* DDI outcome partly ascribed to P-gp inhibition or induction that exceeds 20% change in AUC.
[2] These drugs have in vivo DDI outcomes (i.e., inhibition resulting in ≥2x increase in AUC and partly ascribed to P-gp).
[3] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
[4] Combination ritonavir-boosted regimens are listed here in the DDI memo as strong CYP3A inhibitors (to avoid potential confusion), even though some are considered moderate CYP3A inhibitors in the UW DDI Database.
NTI: Narrow Therapeutic Index
The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (Jan 2021): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine’s “Clinically Relevant” Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington’s Drug Interaction Database (druginteractioninfo.org), and the FDA’s “Guidance for Industry, Drug Interaction Studies”.
This is not a comprehensive list. Please contact the medical monitor with any questions.

10.8 Appendix 8: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

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Glossary

CR	Complete response
CSR	Clinical Study Report
CT	Computed tomography
eCRF	Electronic Case Report Form
FPFV	First patient first visit
ITT	Intent-to-treat
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression

10.8.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document

is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 10.8.2 and the definition of best response in Section 10.8.3.1are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response Section 10.8.3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 10.8.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

10.8.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria by Therasse et al (2000) and revised RECIST guidelines (version 1.1) by Eisenhauer et al (2009).

10.8.2.1 Definitions

10.8.2.1.1 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

Measurable disease - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For participants without measurable disease, even if not expected as per eligibility criteria in this protocol, see Section 10.8.3.2.9

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5 mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥ 15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥ 10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.
- Cystic lesions: Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as

malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same participant, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

10.8.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the participant may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that participants be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how participants with just non-measurable disease at baseline (even if not expected as per eligibility criteria of this protocol) will be evaluated for response and also handled in the statistical analyses is given in Section 10.8.3.2.9

10.8.2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (IV) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of participants, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow- up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a participantis known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow-up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.
- ·A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a major change in technique (e.g. from CT

to MRI, or vice-versa), or a change in any other imaging modality. A change from conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. However, another response assessment than the Novartis calculated UNK response may be accepted from the Investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.

- **FDG-PET:** can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Physical exams**: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions, unless pre-specified by the protocol. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy:** The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers:** Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they

must normalize for a participant to be considered in complete clinical response when all lesions have disappeared.

- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination:** Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

10.8.2.3 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions:** All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the eCRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**:Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 10.8.2.1.1
- **Nodal target:**
  - See Section 10.8.2.1.1

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions:** All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF

10.8.2.4 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 10-10) and non-target lesions (Table 10-11) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 10-12) as well as the presence or absence of new lesions.

10.8.2.4.1 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the Investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

10.8.2.4.2 Determination of target lesion response

Table 10-8 Response criteria for target lesion

Response Criteria	Evaluation of target lesions
Complete Response (CR)	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR)	At least 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters
Progressive Disease (PD)	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm [2]
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR or CR nor and increase in lesions which would qualify for PD
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline [3]

[1.] SOD for CR may not be zero when nodal lesions are part of target lesions
[2.] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3.] In exceptional circumstances an UNK response due to change in method could be over-ruled by the Investigator or central reviewer using expert judgement based on the available information (see Notes on target lesion response and methodology change in Section 10.8.2.2

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the Investigator/radiologist has to decide between the following possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 10-10 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters)
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit

is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an Investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the Investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

10.8.2.4.3 Determination of non-target lesion response

Table 10-9 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR)	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesion must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions [1]
Non-CR/Non-PD	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using different method than baseline [2]

[1.] The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the Investigator or central reviewer does prevail

[2.] It is recommended that the Investigator and/or central reviewer should use expert judgement to assign a Non-UNK response whenever possible (see notes section for more details)

Notes on non-target lesion response

- The Investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e., < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e., ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, 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 disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 10.8.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

10.8.2.4.4 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion eCRF page.

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, then progression should be declared using the date of the first observation of the lesion.

If new disease is observed in a region which was not scanned at baseline or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a participant in which case the response should be UNK, as for any of this participant's assessment Section 10.8.2.4.5

- A lymph node is considered as a "new lesion" and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase
- FDG-PET: can complement CT scans in assessing progression (particularly possible for "new" disease). Section 10.8.2.2

10.8.2.4.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 10-10

Table 10-10 Overall response lesion to each assessment

Target lesions	Non-target lesions	New lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD [1,2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1.] This overall lesion response also applies when there are no non-target lesions identified at baseline
[2.] Once confirmed PR was achieved, all these assessments are considered PR
[3.] As defined in Section 10.8.2.4

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

10.8.3 Efficacy definitions

The following definitions primarily relate to participants who have measurable disease at baseline. Section 10.8.3.2.9 outlines the special considerations that need to be given to participants with no measurable disease at baseline in order to apply the same concepts.

10.8.3.1 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 5 weeks after randomization/start of treatment (and not qualifying for CR or PR
- PD = progression ≤ 13 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD)

- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 5 weeks or early progression within the first 13 weeks)

The time durations specified in the SD/PD/UNK definitions above are defaults based on a 6-week tumor assessment frequency taking into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of Investigator/central blinded review/calculated (Investigator)/calculated (central) overall lesion responses.

Based on the participants' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of participants with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of participants with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize patients with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of participants with a best overall response of CR or PR , or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of participants with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all participants who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Participants with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly, when examining overall response and disease control, participants with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

10.8.3.2 Time to event variables

10.8.3.2.1 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint

10.8.3.2.2 Overall survival

All participants should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

10.8.3.2.3 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a participant has not had an event, time to progression is censored at the date of last adequate tumor assessment.

10.8.3.2.4 PFS2

A recent EMA (2012) guidance recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long-term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

10.8.3.2.5 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study treatment. In some protocols, time to treatment

failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for participants who did not experience treatment failure will be censored at last adequate tumor assessment.

10.8.3.2.6 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows. It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate (specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For participants with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For participants with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For participants with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

10.8.3.2.7 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 10.8.3.2.6. It is recommended that an analysis of all participants (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all participants should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all participants, participants who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options:

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for participants who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case participants have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

10.8.3.2.8 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start Dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 10.8.3.2.8)

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery

10.8.3.2.9 Handling of participants with non-measurable disease only at baseline

It is possible that participants with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any participants with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to participants with measurable disease at baseline, participants without measurable disease should also be incorporated in an appropriate manner. The overall response for participants with non-measurable disease is derived slightly differently according to Table 10-11

Table 10-11 Overall lesion response at each assessment: participants with non-target disease only

Non-target lesions	New lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/Non-PD
UNK	No	UNK
PD	No or Yes	PD
Any	Yes	PD

[1] As defined in Section 10.8.2.4

In general, the **non-CR/non-PD response** for these participants is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response participants with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these participants into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from participants with only non-measurable disease at baseline, handling participants with a best response of CR as "responders" with respect to ORR and all other participants as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all participants with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular participants. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from participants with only non-measurable disease.

10.8.3.2.10 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 10.8.3.2.7and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer and Biologics 2005) as a reference, the following analyses can be considered:

Table 10-12 Options for event dates used in PFS, TTP, duration of response

Situation	Options for end-date (progression or censoring)[1] (1)= default unless specified differently in the protocol or RAP	Outcome
A	(1) Date of randomization/start of treatment[3]	Censored
B	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	(1) Date of last adequate assessment	Censored
E	(1) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	(1) Ignore the new anticancer therapy and follow the situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anticancer therapy(4) Date of secondary anticancer therapy	As per above situations Censored CensoredEvent
G	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1.] Definitions can be found in Section 10.8.3.2.7
[2.] After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 10.8.3.2.7
[3.] The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as participants without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in 5 the “Date of last adequate assessment” by the “Date of previous scheduled assessment (from baseline)”, with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators’ assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

10.8.4 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

10.8.4.1 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

10.8.4.2 End of treatment period completion

Participants **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the Investigator at any time. For participants who are lost to follow-up, the Investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Participants may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

Death is a reason which “must” lead to discontinuation of patient from trial.

10.8.4.3 End of post-treatment follow-up (study period completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Participants may provide study period completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision

- Pregnancy
- Protocol deviation
- Technical problems
- Participant/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

10.8.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local Investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore consequently discrepancy between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local Investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the Investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the Investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the Investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only participants with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

10.8.4.5 Programming rules

The following should be used for programming of efficacy results:

10.8.4.5.1 Calculation of time to event variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

10.8.4.5.2 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 10.8.3.2.7. If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

10.8.4.5.3 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

10.8.4.5.4 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

10.8.4.5.5 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

10.8.4.5.6 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available
- Event documented after two or more missing tumor assessments (optional, see Table 10-12)
- Death due to reason other than underlying cancer (only used for TTP and duration of response)

- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 10.8.3.2.7 This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when participants are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off)
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment
- This reason will also be used to censor in case of no baseline assessment

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