NOVARTIS

Clinical Development

JDQ443

CJDQ443B12201 / NCT05445843

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 mutant non-small cell lung cancer with PD-L1 expression < 1% or a PDL1 expression ≥ 1% and an STK11 co-mutation

Statistical Analysis Plan (SAP) Amendment 2

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30-Nov-2022	Prior to DB lock	Creation of final version	N/A – First version	NA
10-July-2023	Prior to DB lock	[redacted]	SAP Amendment 1	[redacted]
		Added clarification of endpoints for subgroup2.		Section 2.2.1
		Added safety analysis for STK11		Section 2 Beginning
		Added time to first occurrence of AESI (any grade and grade ≥ 3) and duration of first occurrence of an AESI (any grade and grade ≥ 3).		Section 2.9.1
19-Feb-2024	Prior to DB lock	Updated "center" to "site"	SAP Amendment 2	Section 2.1.2 Section 2.2.1 Section 2.3.1 Section 2.4
		Added more details for baseline measurements.		Section 2.1.3.7
		Added "Last contact date" section.		Section 2.1.3.10
		Removed "randomization".		Section 2.2
		Added subgroup analysis for safety.		Section 2.2.1
		Removed summary for retrospective central testing for patients enrolled based on local testing. And clarified the baseline biomarker summary.		Section 2.3.4
		Added details for dose reduction derivation.		Section 2.5.1.4
		Use "start" date instead of		Section

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		"end" date to summarize prior anti-neoplastic medications.		2.5.2.1
		Moved the paragraph about swimmer plot from section 2.7.2 to section 2.8.1.		Section 2.7.2 Section 2.8.1
		Added "+1" for TTR analysis.		Section 2.8.1.3
		Added more details of how to handle missing grade adverse events.		Section 2.9.1.2
		Removed "SOC" for AESI. Added censoring rules for time to first occurrence of AESI.		Section 2.9.1.4
		Added descriptive analysis by timepoint for ΔQTcF. Clarified LVEF analysis.		Section 2.9.4.1
		Added shift tables of ECOG performance status at baseline to worst post-baseline ECOG performance status.		Section 2.9.4.3
		Added PK analysis for all participants.		Section 2.10
		Added the definition of period for death event in the PRO time-to-event analysis. Updated censoring rule for patients with no baseline PRO assessments.		Section 2.11.1
		Removed "The above imputations are only used for analyses of time to and duration of AEs, concomitant medications, and other safety assessments".		Section 4.1.2
		Added "from survival eCRF page" in the title. Removed DCO given last contact date definition.		Section 4.1.4

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
ANP	Antineoplastic
ATC	Anatomical therapeutic classification
AUC	Area under the curve
BIRC	Blinded independent review committee
BOR	Best overall response
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CxDy	Cycle x Day y (C1D1, C5D1, etc.)
DAR	Dose administration record
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern cooperative oncology group performance score
eCRF	Electronic case report form
eCRS	Electronic case retrieval sheet
eDISH	Evaluation of drug-induced serious hepatotoxicity
EORTC	European organisation for research and treatment of cancer
EOT	End of treatment
[redacted]	[redacted]
FAS	Full analysis set
FPAS	Full pharmacokinetic analysis set
FPFV	First patient (participant) first visit
GHS	General health status
IA	Interim analysis
ICF	Informed consent (form)
LATA	Last adequate tumor assessment
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
LPLV	Last patient (participant) last visit
MedDRA	Medical dictionary for drug regulatory affairs
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition
NE	Not evaluable
NMQ	Novartis MedDRA query
NSCLC	Non-small cell lung cancer
NSCLC-SAQ	Non-small cell lung cancer symptom assessment questionnaire

ORR	Overall response rate
OS	Overall survival
PAS	Pharmacokinetic analysis set
PD	Progressive disease
PDI	Planned dose intensity
PF	Physical functioning
PFS	Progression-free survival
[redacted]	[redacted]
PK	Pharmacokinetics
PO	Per os
PPoS	Predictive probability of success
PR	Partial response
PRO	Patient-reported outcomes
PT	Preferred term
QLQ-C30	Quality of life questionnaire, core (30 item)
QoL	Quality of life
QTcF	QT interval corrected with Fridericia's formula
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SMQ	Standardized MedDRA query
SOC	System organ class
TTDD	Time to definitive deterioration
TTR	Time to response
ULN	Upper limit of normal
VAS	Visual analog scale
WHO	World health organization

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for the Clinical Study Report (CSR) of Study CJDQ443B12201, 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 mutant non-small cell lung cancer with PD-L1 expression < 1% or a PD-L1 expression ≥ 1% and an STK11 co-mutation.

As specified in Section 9 of the study protocol, the primary analysis will be performed separately for each of the two cohorts (A and B), when participants in the respective cohort will have completed at least 4 tumor assessments (approximately 24 weeks) or discontinued study treatment prior to that same time due to any cause, provided the cohorts were not discontinued at the futility interim analysis. The results will be reported in a CSR.

Analyses planned for additional data collected past the data cut-off date for the primary analysis, if applicable, will be described in a separate SAP and the results presented in a CSR.

A futility interim analysis (IA) is planned separately for each of the two cohorts. The analyses for the IA will be described in a separate SAP.

The content of this SAP is based on the CJDQ443B12201 clinical study protocol version 00. All decisions regarding the analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study 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-mutant NSCLC (Figure 1-1).

The study will have 2 non-comparative cohorts that will enroll approximately 120 participants (if none of the cohort is stopped for futility) in parallel according to the following characteristics:

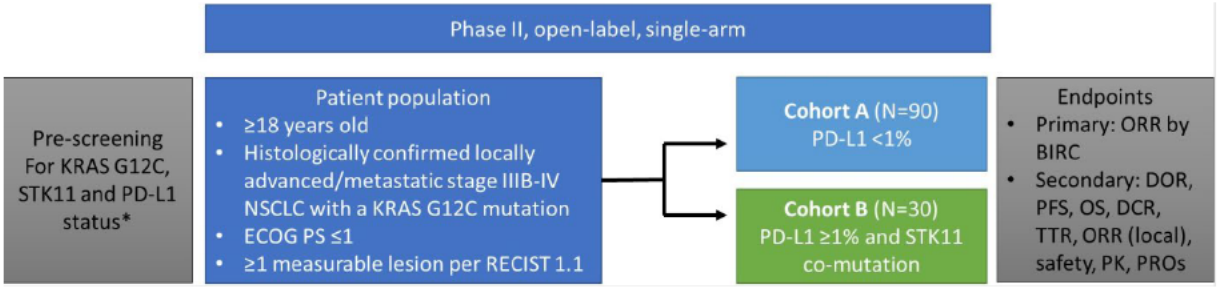
- Cohort A: participants whose tumors harbor a KRAS G12C mutation and a PD-L1 expression < 1%, regardless of STK11 mutation status (N=90).
- Cohort B: participants whose tumors harbor a KRAS G12C mutation, a PD-L1 expression ≥ 1% and an STK11 co-mutation (N=30).

These biomarker characteristics will be determined by a local or central (from a Novartis-designated central laboratory) test result that is positive for the presence of the KRAS G12C mutation, for PD-L1 expression status and for cohort B only, the presence of an STK11 mutation.

Participants who have local documentation of the status of all required biomarkers will be allowed to simultaneously sign the molecular prescreening ICF and main ICF, begin screening procedures, and enrolled provided all inclusion and exclusion criteria are met. A tissue and blood sample must be submitted to the Novartis designated central laboratory for retrospective biomarker testing.

Participants who do not have local documentation on the status of all required biomarkers must have their tissue and/or blood sample tested by the Novartis-designated central laboratory prior to entering main screening.

Figure 1-1 Study design



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 mutant participants are expected from cohort A, hence the STK11 mutant group should have approximately 60 participants.

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 (additional details are provided in the CJDQ443B12201 clinical study protocol).

One interim analysis for futility to assess ORR by BIRC independently in each cohort is planned, when approximately the first 30 (cohort A) and approximately the first 15 participants (cohort B) have been enrolled and followed for at least 2 tumor assessments or have discontinued the study treatment earlier. The primary intent of the interim analyses is to allow an early assessment of the antitumor activity of JDQ443 and to discontinue the respective cohort early if lack of efficacy (futility) is observed. In case the IA of the two cohorts occurs at a similar time, the IAs will be reported together.

1.2 Study objectives, endpoints and estimands

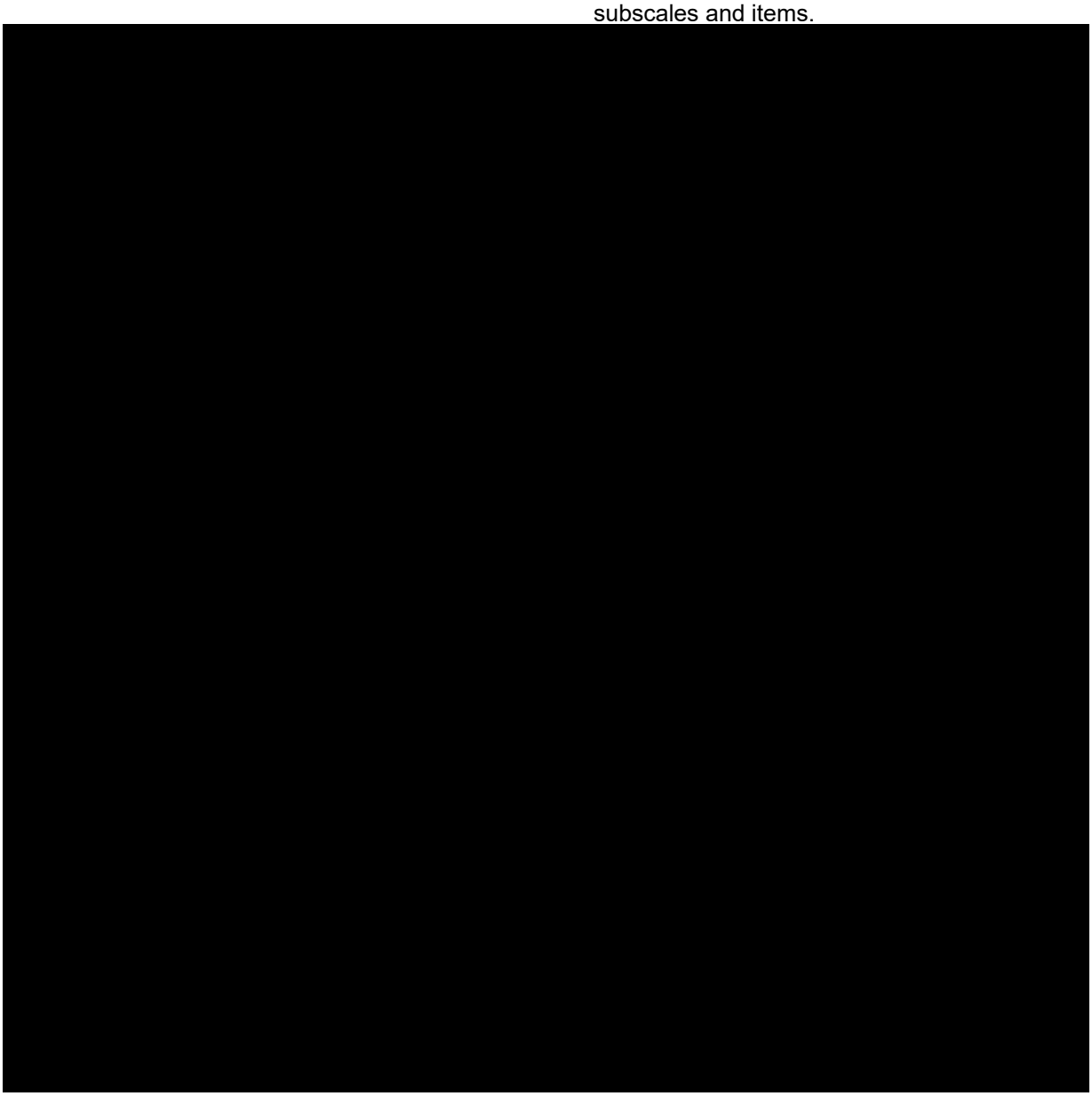
The study objectives and endpoints are described in Table 1-1. All objectives described in the table below will be assessed in both cohorts (A and B), unless specified otherwise in the respective objective.

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary 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 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).

Objectives	Endpoints
Key secondary objectives	**Endpoints for key secondary objectives**
• 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 objectives	**Endpoints for key secondary objectives**
• 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.
• 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, TTR and PFS by BIRC and 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, and health status	• Time to definitive deterioration (TTDD) in the NSCLC-SAQ total score and TTDD in the physical functioning (PF) scale of the EORTC QLQ-C30.

Objectives	Endpoints
	• Change from baseline to each treatment visit and EOT for NSCLC-SAQ total score, and for each NSCLC-SAQ items/domains.Change from baseline to each treatment visit and EOT for all EORTC-QLQ-C30 domains, subscales and items.



1.2.1 Primary estimand(s)

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: JDQ443 administered PO 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 nonresponse (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 and a summary of the reasons for 'NE' BOR.

1.2.2 Secondary estimand(s)

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: JDQ443 administered PO 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 whose best overall response by BIRC is CR or PR 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 whose best overall response by BIRC is CR or PR 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.
3. Treatment of interest: JDQ443 administered PO 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.).

2 Statistical methods

The demographic data will be summarized separately for cohort A, cohort B, the STK11-mutant participants pooled from the two cohorts, and all participants.

The efficacy analyses will be performed separately for each of the two cohorts and the STK11-mutant participants pooled from the two cohorts.

The safety analyses will be presented for cohort A, cohort B, STK11 mutant participants, and all participants.

2.1 Data analysis general information

The primary and final analyses will be performed by Novartis. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings. The futility interim analyses will also be performed by the Novartis team. Details and specifications for the analyses will be provided in an interim analysis plan.

2.1.1 Data included in the analysis

Data from all participants who signed the main informed consent will be used in the analysis. Data collected after participants' withdrawal of informed consent for further participation in the study will not be reported (except for death date, if it is obtained from public records [registers], local law and participant informed consent permitting). The date on which a participant withdraws full consent is recorded in the eCRF.

A cut-off date will be established for the primary analysis after the participants in the respective cohort who are still receiving study treatment will have completed at least 4 tumor assessments or discontinued study treatment earlier. If this criterion is reached earlier in one of the cohorts, the cut-off date and the primary analysis may occur at different times.

All statistical analyses will be performed using all data collected in the database up to the data cut-off date (per cohort, if applicable). All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having a documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these cases, the end date will not be imputed and therefore will not appear in the listings.

2.1.2 General analysis conventions

Pooling of sites: Unless specified otherwise, data from all study sites will be pooled for the analysis. Due to the expected small number of participants enrolled at sites, no site effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of participants in the relevant analysis set or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (e.g. mean, standard deviation, median, percentiles, minimum, and maximum).

2.1.3 General definitions

2.1.3.1 Cohort assignment

The cohort of the participant will be assigned based on the entry in the "Study Treatment Assignment" eCRF.

2.1.3.2 Investigational drug and study treatment

Investigational drug as well as investigational treatment will be used to refer to JDQ443. The term investigational treatment may also be referred to as study treatment which is used throughout this document.

2.1.3.3 Date of first administration of study treatment

The date of first administration of study treatment is defined as the first date when a non-zero dose of study treatment is administered and recorded on the "Study Treatment" eCRF. For the sake of simplicity, the date of first administration of study treatment is also referred to as the start date of study treatment.

2.1.3.4 Date of last administration of study treatment

The date of last administration of the study treatment is defined as the last date when a non-zero dose of study treatment is administered and recorded on the "Study treatment" eCRF. This date will also be referred as last date of study treatment.

2.1.3.5 Study day

The study day describes the day of the event or assessment date, relative to the reference start date (start date of study treatment).

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, PK, PRO, etc.) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

2.1.3.6 Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

2.1.3.7 Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment.
If labs with duplicate laboratory measurements taken at the last assessment date on or before the start date of study treatment, then the rule described below will be applied for the calculation of baseline.
If values are from central and local laboratories, the value from central assessment should be considered as baseline.
For gradable labs:

- The value of lower CTCAE grade will be considered as the baseline value.
- If several records have the same absolute grade, but in different directions, two baselines should be created, the record with grade below 0 should be the baseline of the 'Hypo' parameter, and the other record should be the baseline for the 'Hyper' parameters.

For non-gradable labs:

- If both within normal range: take average value
- If one within normal range and the other outside: take the one within normal range
- If both outside normal range: take the one closest to the normal range

If participants have no value as defined above, the baseline result will be missing.

2.1.3.8 On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of participants informed consent to the day before first administration of study treatment

2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 31 after last administration of study treatment.

Safety summaries (tables, figures) and summaries of on-treatment deaths 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, all deaths which occurred during the study (i.e. during the on-treatment, and post-treatment periods) will be summarized.

An on-treatment adverse event (or treatment-emergent AE) is defined as any adverse event reported in the on-treatment period.

An on-treatment assessment is defined as any assessment performed during the on-treatment period.

In case at the time of the analysis, the date of last administration of study treatment is missing, on-treatment adverse events/assessments include any adverse event/assessment recorded in the database and which occur after the start date of the study treatment.

Data listings will include all assessments/events, flagging those which were collected during the pre-treatment and post-treatment period.

2.1.3.9 Windows for multiple assessments

In order to summarize data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is available in the same time window, the assessment closest to the planned date will be used. If 2 assessments within a time window are equidistant from the target date, then the earlier of the 2 assessments will be used. If there are multiple assessments on the same date, then the worst case will be used.

The following tables define time windows for descriptive summary of PRO (Table 2-1 to Table 2-4) and ECOG performance status (Table 2-1) data by visit and longitudinal data analysis planned in Section 2.11.

Table 2-1 Time windows for ECOG PS

Assessment	Target study day of assessment	Time interval
Baseline	≤ 1	≤ Study days 1
Cycle 2 Day 1	22	Study days 2 to 32
Cycle 3 Day 1	43	Study days 33 to 53
Cycle k Day 1 (k≥ 4)	d=(k−1)×21+1	Study days d−10 to d+10 For last cycle of dosing: from (k−1)×21–9 to EOT disposition date + 7 days Note: EOT visit data are included if obtained within 7 days of

Assessment	Target study day of assessment	Time interval
		permanent discontinuation of study treatment.
Safety follow-up	EOT + 30	From EOT disposition date + 8 days to 44 days after the EOT disposition date

Table 2-2 Time windows for PRO: NSCLC-SAQ, [redacted], [redacted], [redacted] [redacted]

Time window	Planned visit timing	Time window definition
Baseline	≤ 1*	≤ Study day 1*
On treatment		
Cycle 1 Day 8	8	Study days 2 – 11
Cycle 1 Day 15	15	Study days 12 – 18
Cycle 2 Day 1	22	Study days 19 – 25
Cycle 2 Day 8	29	Study days 26 – 32
Cycle 2 Day 15	36	Study days 33 – 39
Cycle 3 Day 1	43	Study days 40 – 46
Cycle 3 Day 8	50	Study days 47 – 53
Cycle 3 Day 15	57	Study days 54 – 60
Day 1 of every cycle from Cycle 4		
Cycle 4 Day 1	64	Study days 61 – 74
Cycle 5 Day 1	85	Study days 75 – 95
Cycle k Day 1 (k = 4, 5, ...)	d = (k−1)×21+1	Study days (k−1)×21−9 to (k−1)×21+11 For last cycle of dosing: from (k−1)×21−9 to EOT disposition date +7 Note: EOT visit data are included if obtained within 7 days of permanent discontinuation of study treatment.
Post treatment		
Efficacy follow-up, every 12 weeks		
Efficacy follow-up 1	12 weeks after EOT disposition date + 7 days	From EOT disposition date + 8 days to 18 weeks after EOT disposition date + 7 days
Efficacy follow-up 2	24 weeks after 24 weeks after EOT disposition date + 7 days	From 18 weeks after EOT disposition date + 8 days to 30 weeks after EOT disposition date + 7 days
Efficacy follow-up k (k = 3, 4, …)[$]	12+(k−1)×12 weeks after EOT disposition date + 7 days	From (k−1) ×12+6 weeks after EOT disposition date + 8 days to (k−1) ×12+18 weeks after EOT disposition date + 7 days

Time window	Planned visit timing	Time window definition
Post disease progression		
Survival follow-up 1	12 weeks after disease progression date	From PD date# to 18 weeks after PD date#
Survival follow-up 2	24 weeks after disease progression date	From 18 weeks after PD date# + 1 day to 30 weeks after PD date#
Survival follow-up 3	36 weeks after disease progression date	From 30 weeks after PD date# + 1 day to 42 weeks after PD date#
Survival follow-up k if available (k = 4, 5, ...)	12×k weeks after disease progression date	From 12×k−6 weeks after PD date# + 1 day to 12×k + 6 weeks after PD date#

* Study day 1 = date of first treatment, C1D1

Post treatment study day 1 = end of treatment date + 1 day

$ The assessment “at disease progression” in efficacy follow-up should be the last visit in this period

It is the EOT visit date + 8 days for participants without efficacy follow-up

Table 2-3 Time windows for PROs: EORTC QLQ-C30

Time window	Planned visit timing	Time window definition
Baseline	On or before Study Day 1*	≤ Study Day 1*
On treatment		
Cycle 2 Day 1	Study Day 22	Study Days 2 32
Cycle 3 Day 1	Study Day 43	Study Days 33 53
Cycle k Day 1 (k≥ 4)	Study day d=(k−1)×21+1	Study days d−10 to d+10 For last cycle of dosing: from (k−1)×21−9 to EOT disposition date + 7 days Note: EOT visit data are included if obtained within 7 days of permanent discontinuation of study treatment.
Post treatment		
Efficacy follow-up, every 12 weeks		
Efficacy follow-up 1	12 weeks after EOT disposition date + 7 days	From EOT disposition date + 8 days to 18 weeks after EOT disposition date + 7 days
Efficacy follow-up 2	24 weeks after EOT disposition date + 7 days	From 18 weeks after EOT disposition date + 8 days to 30 weeks after EOT disposition date + 7 days
Efficacy follow-up k (with k = 3, 4, …)	12+(k−1)×12 weeks after EOT disposition date + 7 days	From (k−1)×12+6 weeks after EOT disposition date + 8 days to (k−1)×12+18 weeks after EOT disposition date + 7 days

Time window	Planned visit timing	Time window definition
After disease progression		
Follow-up 1 after disease progression	12 weeks after disease progression date	From PD date# to 18 weeks after PD date#
Follow-up 2 after disease progression	24 weeks after disease progression date	From 18 weeks after PD date# + 1 day to 30 weeks after PD date#
Follow-up 3 after disease progression	36 weeks after disease progression date	From 30 weeks after PD date# + 1 day to 42 weeks after PD date#
Follow-up k after disease progression (k = 4, 5, ...)	12×k weeks after disease progression date	From 12×k−6 weeks after PD date# + 1 day to 12×k+6 weeks after PD date#

* Study Day 1 = date of first treatment, C1D1

Post treatment study day 1= end of treatment date + 1 day

It is the EOT visit date + 8 days for participants without efficacy follow-up

[redacted]

2.1.3.10 Last contact date

The last contact date will be derived for participants not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-5 Last contact date

Source data	Conditions
Last contact date/last date participant was known to be alive from Survival Follow-up page	Participant status is reported to be alive, lost to follow-up or unknown
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor assessment date	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the participant was seen or contacted on that date. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF.

The last contact date will be used for censoring of participants in the analysis of overall survival.

2.2 Analysis sets

Participants are considered to be enrolled into the study if they have signed the main informed consent. Only participants who have signed the main informed consent will be included in the analysis data sets.

Participants who signed a molecular pre-screening informed consent form but failed to meet pre-screening criteria, as well as participants who signed the main informed consent form and were subsequently found to be ineligible (have failed to meet inclusion or exclusion criteria) will be considered screen failures.

Full Analysis Set

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. Participants will be analyzed according to the cohort they have been assigned to. Participants may be enrolled based on PD-L1 expression status and the presence of a KRAS G12C mutation and STK11 mutation (cohort B only) determined by a validated local test or a central test in tumor tissue or blood.

Safety Set

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.

Pharmacokinetic Analysis Set

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

The criteria 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

Full Pharmacokinetic Analysis Set

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

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

PK blood samples with missing collection date or time or missing associated JDQ443 dosing date or time will be excluded.

Additionally, a PK sample can be considered not evaluable as per scientific judgment of the clinical pharmacology expert. In such case, the PK sample will be excluded from the analyses and the reason for its exclusion will be documented.

2.2.1 Subgroups of interest

No formal statistical test of hypotheses will be performed for the subgroups.

Subgroup 1: Pooled group of participants with STK11 mutation tumors

Participants in the FAS from cohort A and cohort B, whose tumors harbor an STK11 mutation (irrespective if the enrollment was based on local or central testing), will be pooled and analyzed as a subgroup ("STK11 pooled group"). Depending on the number of local-central discordant cases, an additional subgroup may be analyzed with only participants with centrally confirmed mutation.

The endpoints for the secondary objectives for this pooled group will comprise ORR, DOR, DCR, TTR, and PFS by BIRC and local radiology assessment as well as OS.

Subgroup 2: Biomarker subgroups based on KRAS G12C, STK11 and/or PD-L1 status

The following subgroups of the FAS will only be analyzed for cohort A and the STK11 pooled group for efficacy endpoints. Due to the small number of participants in cohort B, subgroup categories are expected to be too small to allow reasonable conclusions.

Cohort A – subgroups based on KRAS G12C mutation status in tissue and blood

a. Participants with both presence of a KRAS G12C mutation and PD-L1 expression < 1% centrally confirmed in tumor tissue, irrespective of the test type (central versus local) and sample type (blood versus tissue) used for eligibility.
b. Participants enrolled based on a blood test for KRAS G12C, irrespective if the enrollment was based on local or central testing and irrespective of the retrospective central result.

STK11 pooled group

c. Participants with the presence of both a KRAS G12C and a STK11 mutation centrally confirmed in tumor tissue, irrespective of the test type (central versus local) and sample type (blood versus tissue) used for KRAS G12C status determination for eligibility.
d. Participants with a STK11 mutation who enrolled based on a blood test for KRAS G12C, irrespective of local or central testing and irrespective of the retrospective central result.

The endpoints for subgroup 2a-2d will comprise ORR, DOR, DCR, TTR, and PFS by BIRC and local radiology assessment as well as OS.

Analyses of additional subgroups based on the biomarkers may be included in the CSR or provided outside of the CSR, if deemed appropriate.

Subgroup 3: Chinese and non-Chinese participants

PK data will be analyzed separately for Chinese participants, i.e. participants from sites in China, and non-Chinese, from all other sites (see Section 2.10).

Subgroup 4: Baseline characteristics subgroups for efficacy

Analyses for subgroups based on baseline characteristics will only be performed for cohort A. The number of participants in cohort B is considered too small to provide reliable results for subgroups.

Subgroup analyses for ORR and PFS (see Section 2.6.6.2, Secton 2.8.1.4) to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed for the following subgroups (based on the FAS):

a. Age (< 65 years vs. ≥ 65 years)
b. Gender (male vs. female)
c. ECOG status (0 vs. 1)
d. Smoking status (never smoker vs. combination of current smoker and former smoker)
e. STK11 mutation status (yes vs. no)
f. KEAP1 mutation status (yes vs. no)
g. Presence of brain metastases at baseline based on BIRC assessment (yes vs. no)
h. Race (Asian vs. Non-Asian)

Subgroup 5: Baseline characteristics subgroups for safety

Key safety analyses will be repeated on safety set for the following subgroups. The objective for carrying out these subgroup analyses is to identify potential safety issues that may be limited to a subgroup of participants, or safety issues that are more commonly observed in a subgroup of participants.

a. Age (< 65 years vs. ≥ 65 years)¬¬
b. Gender (male vs. female)
c. ECOG status (0 vs. 1)
d. Smoking status (former vs current vs never)
e. STK11 mutation status (yes vs. no)
f. KEAP1 mutation status (yes vs. no)
g. Presence of brain metastases at baseline based on BIRC assessment (yes vs. no)
h. Race (Asian vs. Non-Asian)

The following safety summaries will be performed by subgroup:

- AEs, regardless of study treatment, by preferred term and maximum CTC grade
- AEs with suspected relationship to study drugs by preferred term and maximum CTC grade

2.3 Participant disposition, demographics and other baseline characteristics

The FAS will be used for all participant demographic and baseline characteristic summaries and listings unless otherwise specified. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

2.3.1 Enrollment status

The number and percentage of participants enrolled will be summarized by country, site, and cohort.

In addition, the number of participants screened will be summarized by country and site. For subjects who are screen failures, the reasons for not completing screening will be summarized based on the "Disposition" eCRF.

2.3.2 Basic demographic and background data

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by cohort. Categorical data will be presented as frequencies and percentages.

Body mass index [kg/m^2] will be calculated as weight [kg] / (height $[m]^2$) using weight and height at baseline.

2.3.3 Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include primary site of cancer, tumor histology, time (in months) since initial diagnosis, stage at initial diagnosis, time (in months) from initial diagnosis to first recurrence/progression, time (in months) since most recent relapse/progression, stage at time of study entry, number and type of metastatic sites, as well as disease burden (sum of target lesion diameters at baseline, based on BIRC and investigator assessment). Metastatic sites will be based on the "Diagnosis and Extent of Cancer" eCRF. Data on diagnosis and extent of cancer will also be listed.

2.3.4 Biomarker status

The biomarker test type (central versus local) and sample type (tissue versus blood) used for status determination for eligibility will be summarized per biomarker. A summary of the biomarker status (mutation or expression level) between local (based on tumor or plasma) and central testing (based on tumor) will be provided. Details of the biomarker testing and results will be listed.

When multiple testing types and sample types are available, the biomarker status in the geographic table follows:

1. If both tumor and plasma samples are available, testing results based on the tumor will be used.

2. If both local and central testing are available, the patient will be considered a mutant if either local or central testing is positive.in

2.3.5 Medical history

Relevant medical histories and current medical conditions at baseline will be summarized and listed. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

2.3.6 Analysis sets

The number and percentage of participants in each analysis set will be summarized. Reasons for exclusion of participants from analysis sets will be tabulated.

2.3.7 Screening phase disposition

Screen failures recorded in the screening phase disposition will comprise participants who signed the molecular pre-screening ICF and were screen failed or were screened but were not enrolled into the study. Frequency counts and percentages will be tabulated for all enrolled participants as follows:

- Number (%) of participants ongoing in the screening phase.
- Number (%) of participants who completed the screening phase
- Number (%) of participants who discontinued during the screening phase (participants did not continue into the next phase of the study)
- Reasons for screening phase discontinuation

All screen failure participants with reasons for screen failure will be listed.

2.3.8 Participant disposition

For the participant disposition summary table, the following information (and potentially additional subcategories) will be presented:

Participants enrolled:

- Number (%) of participants treated
- Number (%) of participants not treated

Related to the on-treatment period:

- Number (%) of participants who are still on-treatment
- Number (%) of participants who discontinued treatment and continued in the follow-up period
    - Primary reasons for study treatment discontinuation
- Number (%) of participants who discontinued the study

Related to the post-treatment period:

- Number (%) of participants who are still in the follow-up period
- Number (%) of participants who discontinued from the post-treatment follow-up period
  - Primary reasons for discontinuation from the post-treatment follow-up period

The information will be derived from the applicable "Subject status" and "Disposition" eCRFs. The disposition information will also be listed.

2.4 Protocol deviations

The number and percentage of participants in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the edit checks specification document). All protocol deviations will be listed.

In addition to the pre-defined standard PD terms, Novartis has defined 6 new protocol deviations and the corresponding relationship (health status related, site lockdown, patient concerns, drug supply issue etc.) to the COVID-19 pandemic in line with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (Food and Drug Administration 2021) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (European Medicines Agency 2022). The following deviations related to the COVID-19 pandemic will be summarized.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Participant discontinuation due to COVID-19 situation

A cross-tabulation of COVID-19 related PD vs. relationship will also be produced. In addition, COVID-19 related outcomes (e.g., COVID-19 AEs, discontinuation due to COVID-19, death due to COVID-19) will be descriptively summarized by country, sites, and cohort.

2.5 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The safety set will be used for all medication data summaries and listings unless otherwise specified.

2.5.1 Study treatment / compliance

Duration of exposure to study treatment, cumulative dose, dose intensity (DI), and relative dose intensity (RDI) will be summarized for the on-treatment period. The duration of exposure will be categorized into time intervals (< 6, ≥ 6–< 12, ≥ 12–< 24, ≥ 24–< 48, ≥ 48 weeks); frequency counts and percentages will be presented for the number of participants in each interval. A categorical summary of the RDI will be presented ($\leq 75\%$, $> 75\%$–$\leq 90\%$, $> 90\%$–$\leq 110\%$, $> 110\%$).

The number (%) of participants who have dose reductions, interruptions, and the respective reasons, and the number (%) of participants who have dose escalation for one dose level after dose reduction will be summarized in the on-treatment period.

Participant level listings of all doses administered on treatment along with dose change reasons will be generated. A listing of participants receiving study drug from specific batches (for CSR appendix 16.1.6) will also be generated.

2.5.1.1 Duration of exposure

Duration of exposure to study treatment is defined as:

- Duration of exposure to study treatment (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1;
- Duration of exposure to study treatment (weeks) = (duration of exposure to study treatment)/7.

The last date of exposure to study treatment is defined in Section 2.1.3.4. The duration includes periods of temporary interruption.

2.5.1.2 Cumulative dose

Cumulative dose is defined as the total dose given during the study treatment exposure and will be summarized for each cohort. For participants who did not take any study treatment the cumulative dose is by definition equal to zero.

The cumulative dose is calculated using the information from the "Study Treatment" eCRF and is expressed in mg. The cumulative dose is the sum of the non-zero doses recorded over the dosing period.

2.5.1.3 Dose intensity and relative dose intensity

Dose intensity (DI) is defined for participants with non-zero duration of exposure as follows:

- DI (mg/day) = cumulative dose (mg) / duration of exposure to study treatment (day).

For participants who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is the assigned dose by unit of time planned to be given to participants as per protocol in the same dose unit and unit of time as for dose intensity. Planned dose intensity is 400 mg/day (200 mg b.i.d.).

Relative dose intensity (RDI) is defined as follows:

- RDI (%) = [DI (mg/day) / PDI (mg/day)] × 100

2.5.1.4 Dose reductions, interruptions, or escalations

The number and percentage of participants who had dose reductions or interruptions with the corresponding reasons and the number and percentage of participants who had a dose escalation of one dose level after a dose reduction will be summarized. Permanent discontinuations of study treatment will be summarized in the disposition table.

The duration of the dose interruption will be summarized by time intervals in weeks for each observed interruption (< 1 week, 1–2 weeks, 2–3 weeks, ...) as well as by descriptive statistics. The time intervals may be adjusted depending on the observed data. The duration of a dose interruption is defined as (start date of the first dose administration after interruption − start date of the dose interruption).

The "Dose interrupted" and "Dose change" option from the type of change field of the "Study Treatment" eCRF will be used to determine the dose interruptions and dose changes (reductions, escalations) respectively. The corresponding fields "Reasons for dose change" from the "Study Treatment" eCRF will be used to summarize the reasons.

Interruption: An interruption is defined as a dose of zero given on one or more days between two non-zero dosing records.

For the purpose of summarizing interruptions and reasons, any two or more consecutive zero doses will be counted as one interruption if the reasons for these two consecutive dose interruptions are the same. They will be counted as two different interruptions only if the reasons are different. If an interruption occurs for more than one day due to the same reason, but the days are not consecutive, i.e., there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence. For participants who have dose interruption checked on the eCRF but never resume a non-zero dose, the dose interruption will not be counted.

Dose reduction: A dose reduction is defined as a decrease of the total daily dose from the protocol planned starting dose (200 mg b.i.d.) to another non-zero dose or a decrease from the previous dose that is less than the protocol planned starting dose to another non-zero dose, even if the decrease has been directly preceded by an interruption.

The number of dose reductions will be derived programmatically based on the change and the direction of the change.

- If a participant received less than the protocol planned dose (nonzero) for one day without any reason, then this is not a dose reduction. This applies to the first dosing record.
- If, due to a dosing error, a participant receives higher than protocol planned dose and moves down to the planned dose then this is not a dose reduction. However if the change is directly from a higher than planned dose down to a lower than protocol planned dose, then this is a dose reduction.
- If due to interruption, a participant receives less than the previous total daily dose for 1 day and **followed** by an interruption (due to the same reason) then this is NOT a dose reduction. If due to interruption, a participant receives less than previous total daily dose for 1 day **after** an interruption (due to the same reason) then this is NOT a dose reduction. After interruption, dose reduction will be determined using the dose received on a day not related to interruption.
- If a patient receives half of the dose **on the last day** of treatment (for ex: 200 mg BID from 30-May-2023 to 03-Oct-2023, and 200 mg QD on 04-Oct-2023), then this is

NOT a dose reduction. This rule is applied for any dose levels (for ex: 100 mg BID from 15-Dec-2023 to 20-Dec-2023, and 100 mg QD on 21-Dec-2023).

For examples of dose change, refer to the eCRF completion guidance document.

Dose escalation: A dose escalation is defined as an increase to the next higher dose level after the participant had a dose reduction. According to study protocol section 6.5.1 a participant is only allowed to have one such escalation.

2.5.2 Prior, concomitant and post therapies

2.5.2.1 Prior anti-cancer therapy

The number and percentage of participants who received any prior anti-neoplastic (ANP) medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized using the FAS.

Prior anti-neoplastic medications will be summarized by therapy type (e.g., chemotherapy, immunotherapy, etc.), setting (e.g., adjuvant, neo-adjuvant), number of prior regimens of anticancer medications, therapy type and setting at last medication (based on the last start date of all prior regimen components). The medication therapy type of any combination therapy will be counted in each category. For example, a participant receiving a combination of chemotherapy and immunotherapy will be counted under “chemotherapy” and “immunotherapy”. Prior antineoplastic medications will also be summarized by ATC class, and preferred term.

Anti-neoplastic medications will be coded using the World Health Organization (WHO) Drug Dictionary (WHO-DD). Details regarding the WHO-DD version will be included in the footnotes of the tables and listings.

For radiotherapy, time since last radiotherapy, locations and setting of last therapy will be summarized.

For prior surgery, time since last surgery, procedure and residual disease of last therapy will be summarized.

Separate listings will be produced for prior anti-neoplastic medications, radiotherapy, and surgery.

2.5.2.2 Post-treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by therapy type and number of post-treatment therapies received using the FAS.

Anti-neoplastic medications initiated after discontinuation of study treatment will be listed and summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term.

Anti-neoplastic radiotherapy as well as anti-neoplastic surgery since discontinuation of study treatment will be summarized and listed.

2.5.2.3 Concomitant therapy

Concomitant therapy will be summarized for all interventions (therapeutic treatments, surgeries and procedures) other than the study treatment administered to a participant coinciding with the on-treatment period.

Concomitant therapy includes medications (other than the study treatment) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO ATC classification system and summarized by lowest ATC class and preferred term. These summaries will include

- Medications starting on or after the start date of study treatment but no later than 30 days after the last date of administration of study treatment and
- Medications starting prior to the start date of study treatment and continuing after the start date of study treatment (in the on-treatment period)

In addition, surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start date of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

The safety set will be used for all concomitant therapy tables and listings.

2.6 Analysis supporting primary objective(s)

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). The primary analysis of the primary and key secondary endpoint will be conducted when participants in the respective cohort who are still receiving study treatment will have completed at least 4 tumor assessments or discontinued earlier (approximately 24 weeks), provided that cohort A was not declared futile at the interim analysis.

Depending on the enrollment and follow-up of the participants in the two cohorts, the analysis of the primary and key secondary endpoint can also beanalyzed at the same time.

The analysis will be based on the FAS and will include all participant data observed up to the cut-off date.

2.6.1 Primary endpoint(s)

The primary clinical question of interest and the primary estimand are defined in Section 1.2.1.

The primary endpoint 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. Complete and partial responses 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 (with the exception of protocol-allowed radiotherapy).

The BOR will be determined from response assessments undertaken while on treatment. In addition, only tumor assessments performed before the start of any further anti-neoplastic therapy (with the exception of protocol-allowed radiotherapy) will be considered in the assessment of BOR.

BOR for each participant 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;
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR);
- SD = at least one SD assessment (or better) > 5 weeks after start of treatment (and not qualifying for CR or PR);
- Non-CR/non-PD* = at least one Non-CR/non-PD assessment > 5 weeks after start of treatment (and not qualifying for CR);
- PD = progression ≤ 13 weeks after start of treatment (and not qualifying for CR, PR or SD);
- NE = 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).

* For participants with only non-measurable disease present at baseline. A non-CR/non-PD response is considered equivalent to an SD response for the ORR determination and participants will be considered "non-responders".

Participants with 'NE' BOR will be summarized by reason for having NE status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall lesion response NE
- New anti-neoplastic therapy started before first post-baseline assessment
- SD too early (≤ 5 weeks after start of treatment)
- PD too late (> 13 weeks after start of treatment)

Note 1: An SD is considered as "SD too early"' if the SD is documented within the first 5 weeks after the start of treatment date.

Note 2: A PD is considered as "PD too late" if the first documentation of PD is recorded more than 13 weeks after the start of treatment date with no qualifying CR, PR or SD in between.

Note 3: Special (and rare) cases where BOR is "NE" due to both too early SD and too late PD will be classified as "SD too early".

2.6.2 Statistical hypothesis, model, and method of analysis

The primary efficacy endpoint ORR will be estimated, and the exact binomial 95% confidence interval (CI) (Clopper, Pearson 1934) provided.

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

H_{0A}: ORR [redacted] vs. H_{1A}: ORR [redacted]

The tests will be performed based on the exact binomial CI 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%.

2.6.3 Handling of intercurrent events

The primary analysis will account for different intercurrent events as follows:

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). Protocol-allowed radiotherapy is exempted.
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).

2.6.4 Handling of missing values not related to intercurrent event

The determination of the BOR incorporates missing values including cases of participants with no valid post-baseline assessments.

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.

2.6.5 Sensitivity analyses

Not applicable.

2.6.6 Supplementary analyses

2.6.6.1 Supplementary estimands

A supplementary estimand is defined by the same target population, treatment of interest, intercurrent events, and summary measure as for the primary estimand (see Section 1.2.1). 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 (with the exception of protocol-allowed radiotherapy) considered as non-response.

The method of analysis as well as the handling of intercurrent events and missing data will be the same as described in Section 2.6.2, Section 2.6.3, and Section 2.6.4.

A second supplementary estimand is defined by the same primary variable, treatment of interest, intercurrent events, and summary measure as for the primary estimand (see Section 1.2.1). Differently from the primary estimand, the target population will be participants with both presence of a KRAS G12C mutation and PD-L1 expression < 1% centrally confirmed in tumor tissue, i.e. subgroup 2a.

The method of analysis as well as the handling of intercurrent events and missing data will be the same as described in Section 2.6.2, Section 2.6.3, and Section 2.6.4.

2.6.6.2 Other supplementary analyses

A subgroup analysis of ORR by central and local investigator review will be prepared for cohort A for the subgroups 4a to 4h.

2.7 Analyses supporting key secondary objectives

The key secondary clinical questions of interest and the corresponding estimands are defined in Section 1.2.2.

The key secondary objectives 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) in both cohorts.

As the two 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.

The key secondary efficacy endpoints will be assessed using the FAS.

2.7.1 Key secondary endpoints

The key secondary endpoints are ORR in cohort B as well as duration of response in both cohorts (A and B).

ORR by BIRC for cohort B

ORR per RECIST 1.1 by BIRC in cohort B is defined in the same way as specified in Section 2.6.1.

DOR by BIRC for cohort A and cohort B

Duration of response is defined as the duration of time between the data of first documented response (PR or CR) and the date of the first documented radiological progression or death due to any cause. DOR will be evaluated based on the BIRC assessment.

DOR only applies to participants whose best overall response is CR or PR based on tumor response data per BIRC assessment. If a participant has not had an event, DOR will be censored at the date of the last adequate tumor assessment using the censoring rules described in Table 2-5. Participants who never achieved a BOR of CR or PR will be excluded from the analysis.

2.7.2 Statistical hypothesis, model, and method of analysis

ORR by BIRC for cohort B

The ORR in cohort B will be estimated and the estimate as well as the exact binomial 95% CI will be presented.

Treatment with JDQ443 will be considered to have clinically relevant efficacy in cohort B if an ORR of [redacted] is observed with the lower bound of the 95% CI [redacted] The following statistical hypotheses will be tested:

H_{0B}: ORR [redacted] vs. H_{1B}: ORR [redacted]

The test will be performed based on the exact binomial CI 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 $\geq$ 20%.

DOR by BIRC for cohort A and cohort B

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 by cohort.

2.7.3 Handling of intercurrent events

ORR by BIRC for cohort B

The analysis will account for different intercurrent events as follows:

1. Treatment discontinuation for any reason: Tumor assessment data collected irrespective of treatment discontinuation 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). Protocol-allowed radiotherapy is exempted.

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).

DOR by BIRC for cohort A and cohort B

The analysis will account for different intercurrent events as follows:

1. Treatment discontinuation for any reason: Tumor assessment data collected irrespective of treatment discontinuation will be included to derive DOR (treatment policy strategy).
2. Start of a new anti-neoplastic therapy: If any new anti-neoplastic therapy (with the exception of protocol-allowed radiotherapy) is initiated, progression or death occurring after the use of new anti-neoplastic therapy will not be considered and the DOR will be censored.
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 DOR (treatment policy strategy).

2.7.4 Handling of missing values not related to intercurrent event

ORR by BIRC for cohort B

Participants with no valid post-baseline assessments will be assigned NE and will be included in the BOR derivation.

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.

DOR by BIRC for cohort A and cohort B

DOR events will be included in the analysis if they occur after one missing assessment.

Radiological progression or death observed after 2 or more missing tumor assessments will not be included in the derivation of the time to event for DOR, and the observation will be censored at the time of the last adequate tumor assessment prior to the first missing assessment. Participants without a post-baseline tumor assessment (and without death) will be censored at the time of start of study treatment.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD or non-CR/non-PD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred), the date of start of study treatment will be used.

In particular, DOR will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of "not evaluable (NE)". The rule to determine the number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-5 for censoring and event date options and outcomes for DOR. The same principles also apply for PFS.

Table 2-6 Outcome and event/censor dates for DOR and PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of start of treatment*	Censored
Progression or death at or before next scheduled assessment	Date of progression (or death)	Progressed
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to "Disease progression" without documented progression, i.e., clinical progression based on investigator claim	Ignore the new anticancer therapy and follow situations above	As per above situations
New anticancer therapy given prior to protocol defined progression	Date of last adequate assessment prior to start of new anticancer therapy	Censored
Death before first PD assessment	Date of death	Progressed

*The rare exception to this is if the participant 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

2.7.5 Sensitivity analyses

Not applicable.

2.7.6 Supplementary analyses

Other supplementary analyses comprise ORR per RECIST 1.1 as assessed by the Investigator (local assessment) along with 95% confidence intervals for cohort B and a summary of the reasons for 'NE' BOR, as well as DOR per RECIST 1.1 as assessed by the Investigator (local assessment), for cohort A and cohort B.

An assessment of the concordance between the BIRC assessment and the local assessment of the BOR for each participant will also be provided. The calculation will be based on the percent agreement (the proportion of response outcomes that agree across both independent reviewer and investigator assessments):

Percent Agreement = (Number of matched responders + Number of matched non-responders) / total number of subjects assessed.

2.8 Analyses supporting other secondary efficacy objectives

Other secondary efficacy objectives are:

- To assess the antitumor activity of JDQ443 single-agent as first-line treatment.
- 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).

The antitumor activity will be evaluated by the following endpoints: DCR, PFS, TTR, and OS. The analyses will be based on both central review and Investigator review per RECIST 1.1. The secondary efficacy endpoints will be assessed using the FAS.

2.8.1 Secondary efficacy endpoints

2.8.1.1 Disease control rate

Disease control rate is defined as the proportion of participants with a BOR of confirmed CR, PR, SD, or Non-CR/Non-PD as per Investigator or BIRC assessment based on RECIST 1.1. DCR will be analyzed using the same analytical conventions as for ORR.

2.8.1.2 Visualization of anti-tumor activity

Waterfall graphs will be used to depict the anti-tumor activity. One waterfall graph each will be constructed using the data from the Investigator assessments and the BIRC assessments.

These plots will display the best percentage change from baseline in the sum of diameters of all target lesions for each participant. Only participants with measurable disease at baseline will be included in the waterfall graphs.

Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. As a conservative approach, participants with such assessments will not be represented as bars in the waterfall graph but will be represented by a "zero" bar with a special symbol (e.g., ✶).

Assessments with NE target lesion response and assessments with NE overall response will be excluded from the waterfall graphs. Participants without any valid assessments will also be excluded from the waterfall graphs.

The total number of participants displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of participants with tumor shrinkage and tumor growth. A footnote will explain the reason for excluding some participants (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 2-6.

Table 2-7 Assessments considered for calculation of best percentage change for waterfall graphs

Case	Target response	Overall lesion response	Calculate % change from baseline in sum of diameters?
1	NE	Any	No, exclude assessment
2	Any	NE	No, exclude assessment
3	CR/PR/SD	PD	No, flag assessment with special symbol (✶)
4	PD	PD	Yes
5	CR/PR/SD	CR/PR/SD	Yes

Based on the above considerations, the following algorithm will be used to construct the waterfall graph:

1. Select "valid" post-baseline assessments to be included, i.e., for each participant and each assessment repeat the following four steps.
   a. Check the target lesion response and overall lesion response. If at least one of them is NE, then exclude the whole assessment. Otherwise, go to step 1.b.
   b. Check the overall lesion response. If it is PD then go to step 1.c. Otherwise go to step 1.d.
   c. Check target response. If it is PD then go to step 1.d. Otherwise flag the assessment with a special symbol (✶).
   d. Calculate the % change from baseline in target lesions.
2. For each participant, go through all valid assessments identified in step 1 and find the assessment with best % change from baseline in target lesions. The "best" means best for the participant, i.e., the largest shrinkage or if a participant only has assessments with tumor growth take the assessment where the growth is minimal.
3. Construct the waterfall graph displaying the best % change from baseline for each participant. Participants having only flagged assessment(s) (✶) will be displayed separately.

The BOR will be shown above each of the displayed bars in the waterfall graph, if the number of participants displayed in the graph is small enough for the labels to be legible.

The order of the display from left to right will be as follows:

- Bars under the horizontal axis representing tumor shrinkage;
- Bars above the horizontal axis representing tumor growth;
- "Zero" bars with special symbol (✶).

For each of the 3 categories above, n (%) (where % uses the total number of participants displayed in the waterfall graph) will be displayed. If there are any participants with zero change they will be shown as a separate category following participants with tumor shrinkage.

The swimmer plots will also be used to display the overall response of each participant over time , depicting the onset and duration of the different response categories.

2.8.1.3 Time to response

Time to response is defined as the time from the date of first dose of study treatment to the first documented response (CR or PR, which must be confirmed subsequently). TTR will be evaluated based on Investigator or BIRC assessment according to RECIST 1.1.

All participants in the FAS will be included in TTR calculations. Participants who did not achieve a confirmed CR or PR will be censored at the last adequate tumor assessment date when they did not have a PFS event (i.e. , radiological disease progression or death due to any cause) or at maximum follow-up (i.e., LPLV − FPFV + 1 used for the analysis) when participants had a PFS event.

TTR will be summarized by descriptive statistics 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. TTR data will also be listed.

2.8.1.4 Progression-free survival

Progression-free survival 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 evaluated based on Investigator or BIRC assessment according to RECIST 1.1.

PFS will be censored if no PFS event (radiological progression or death) is observed prior to the first to occur between: (i) the analysis cut-off date, and (ii) the date when a new anti-neoplastic therapy (with the exception of protocol-allowed radiotherapy) 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.

Clinical deterioration will not be considered as documented disease progression. A PFS event date will be included in the analysis if it occurs after one missing tumor assessment. If the PFS event is observed after two or more consecutive missing tumor assessments, PFS will be censored at the last adequate tumor assessment prior to the first missing assessment.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR, SD, or non-CR/non-PD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. Participants without a post-baseline tumor assessment will be censored at the date of first dose of study treatment.

A missing adequate tumor assessment is defined as a tumor assessment (TA) not performed or a tumor assessment with overall lesion response of “not evaluable (NE)”. The rule to determine the number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. Details are described in Section 4.5.

Table 2-5 shows the censoring and event date options and the outcomes for PFS. Details about censoring rules for PFS follow the RECIST 1.1 guidelines ([Study Protocol Section 10.8]) and are provided in Section 4.5.

The distribution of PFS will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curve, median, and 95% CI of the median will be presented by cohort.

A subgroup analysis of PFS will be prepared for cohort A for the subgroups 4a to 4h.

Censoring pattern for PFS

The number of participants censored and the reasons for censoring will be summarized using descriptive statistics and presented separately for Investigator assessment and BIRC assessment.

Concordance analysis of PFS

A cross-tabulation of PFS by BIRC assessment vs. PFS by Investigator assessment by PFS event type (i.e., “death”, “PD”, “censored” for each of the two sources) will be prepared to investigate the discordance between the two sources. The discordance rate (in %) between BIRC and Investigator assessment will be summarized.

A summary table will be produced displaying the PFS timings for the Investigators’ assessment compared to the BIRC assessment. For progression assessments, the frequency and percent of participants with complete agreement (occurring on the same date plus or minus 7 days of each other), progression later, progression earlier, and cases where progression was called by one method and censored by the other will be displayed. Similarly, if censoring was recorded, the frequency and percent of participants with complete agreement, censoring called later, censoring called earlier, and cases where censoring was called by one method and progression was called by the other method will be displayed.

2.8.1.5 Overall survival

Overall survival 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 analysis 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. The OS data will also be listed.

Censoring pattern for OS

The number of participants censored for the OS analysis will be summarized. In addition, a summary of the reasons for OS censoring (“Alive” or “Lost to follow-up”) will be provided.

2.8.2 Analyses for the STK11 pooled group

Participants in the FAS pooled from cohort A and cohort B, whose tumors harbor an STK11 mutation, regardless of PD-L1 expression status, will form the STK11 pooled group (subgroup 1 in Section 2.2.1).

The endpoints for the subgroup are ORR, DOR, DCR, TTR, and PFS by BIRC and Investigator assessment as well as OS. The analysis will follow the same specifications as in Section 2.7.

2.8.3 Listings

Listings for the efficacy endpoints will be provided by cohort and separately for the STK11 pooled group.

2.9 Analyses supporting secondary objectives – safety

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 as defined in Section 2.1.3.8, with the exception of baseline data which will also be summarized where appropriate (e.g., change from baseline summaries). 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). In addition, a separate summary for deaths including on-treatment and post-treatment deaths will be provided.

All safety data, regardless of observation period, will be listed and assessments collected in the post-treatment period will be flagged in the listings.

2.9.1 Adverse events (AEs)

2.9.1.1 General rules for AE reporting

Adverse events which will be counted in summary tables are those that are treatment-emergent. These events have an onset on or after the start of the on-treatment period, or which were present prior to the start of the on-treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the on-treatment period.

2.9.1.2 AE analyses

Summary tables for AEs will include only the treatment-emergent events. AEs will be summarized by system organ class and/or preferred term, and severity (based on CTCAE version 5.0). Separate summaries will be provided for study treatment related treatment-emergent AEs, all deaths, on-treatment deaths, all serious adverse events and treatment-related SAEs, other significant AEs, treatment-related AEs leading to treatment discontinuation, dose adjustment, and additional therapy.

All AEs, deaths, and serious adverse events (including those from the pre- and post-treatment periods) will be listed and those collected during the post-treatment period will be flagged. A listing of AE MedDRA coding will be generated to provide the list of preferred terms that changed as a result of the re-mapping process to the latest MedDRA version.

A participant with multiple adverse events within a SOC will only be counted once towards the total of the system organ class. A participant with multiple occurrences of an AE will be counted only once in the respective AE category. A participant with multiple CTCAE grades for the same PT will be summarized under the maximum CTCAE grade recorded for the event. AEs with missing CTCAE grade will be included in the “All grades” column of the summary tables by grade and will be counted in both ‘missing grade’ and available maximum

grade in the summary tables by maximum grade. An AE wih missing seriousness will be counted as non-serious AE.

In AE summaries, the SOC will be presented alphabetically, and the PT will be sorted within SOC in descending frequency. Summaries by CTCAE grade will present columns for grades 3/4, grade 5, and all grades, as applicable.

In summary, the following AE summaries will be generated:

- AEs regardless of study treatment relationship
- AEs suspected to be study treatment related
- On-treatment deaths, by SOC and preferred term
- All deaths, by SOC and preferred term
- SAEs regardless of study treatment relationship
- SAEs suspected to be study treatment related
- AEs leading to permanent discontinuation of study treatment regardless of study treatment relationship
- AEs leading to permanent discontinuation of study treatment suspected to be study treatment related
- AEs requiring dose adjustment and/or study treatment interruption regardless of study treatment relationship
- AEs requiring dose adjustment and/or study treatment interruption suspected to be study treatment related
- AEs requiring significant additional therapy regardless of study treatment relationship
- AEs requiring significant additional therapy suspected to be study treatment related
- AEs excluding SAEs regardless of study treatment relationship

2.9.1.3 Clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two tables will be provided by SOC and PT based on the safety set:

- On-treatment AEs which are not SAEs with an incidence greater than 5%
- On-treatment SAEs and SAEs suspected to be related to study treatment

If for the same participant, several consecutive AEs (irrespective of study treatment causality, seriousness, and severity) occurred with the same SOC and PT,

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE,
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE/SAE suspected to be related to study treatment/non-SAE has to be checked in a block, e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.9.1.4 Adverse events of special interest / grouping of AEs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to JDQ443. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), high level group terms, high level terms, and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. An NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

All AESI definitions or AE groupings are specified in the electronic Case Retrieval Strategy (eCRS) in which they are identified by the flag "SP". The latest version of the eCRS available at the time of the analysis will be used.

For each specified AESI, the number and percentage of participants with at least one event of the AESI occurring during the on-treatment period will be summarized. The summaries will present grade, SAE, relationship to study treatment, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death etc. A listing of the MedDRA terms that define the AESIs will be generated.

Analysis of time to first occurrence of AESI (any grade and grade ≥3) will be applied using the Kaplan-Meier method. Duration of first occurrence of AESI (any grade and grade ≥3) will also be summarized. These analyses will be performed for AESI regardless of study drug relationship and for AESI suspected to be study drug related. In the absence of an event during the on-treatment period, the censoring date applied will be the earliest of the following dates: date of death, start date of new antineoplastic therapy before experiencing an event, end date of on-treatment period, analysis cut-off date, withdrawal of informed consent date.

All participants who experienced at least one AESI in the Safety set will be included in time to first occurrence of AESI (any grade and grade ≥3) and duration of first occurrence of an AESI calculation.

Duration of first occurrence of an AESI (any grade and grade ≥3) will be presented for the subset of subjects in the safety set who experienced the event. If there is no resolution during the on-treatment period, apatient will be censored at the earliest of the following dates: death date, new anti-neoplastic antineoplastic therapy start date, end date of on-treatment period, analysis cut-off date, and withdrawal of informed consent date.

2.9.2 Deaths

Separate summaries for on-treatment deaths and all deaths will be produced by cohort, primary SOC, and preffered term. All deaths will be listed, and deaths in the post-treatment period will be flagged. A separate listing of deaths prior to start of treatment will be provided for all screened participants.

2.9.3 Laboratory data

For laboratory data assessments, data from all sources (central and local laboratories) will be combined. The summaries will include all laboratory assessments collected in the pre-treatment period (for baseline, if applicable) and on-treatment period. All laboratory assessments will be listed and those collected in the post-treatment period will be flagged in the listings.

For laboratory tests where NCI CTCAE grades are applicable, grading of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values (in SI units) 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, or high based on laboratory normal ranges.

The following summaries/listings will be generated separately for hematology, biochemistry, and cardiac enzymes laboratory data (by laboratory parameter and cohort):

For laboratory tests where grades are defined by CTCAE v5.0:

- Worst post-baseline CTC grade (regardless of the baseline status). Each participant will be counted only for the worst grade observed post-baseline
- Shift tables using CTC grades to compare baseline to the worst on-treatment value (hypo and hyper worst grade will be summarized separately, if applicable)

For laboratory tests where CTC grades are not defined:

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

Listings of all laboratory data by participant and visit/time, with the corresponding CTCAE v5.0 grades, if applicable, and the classifications relative to the laboratory normal ranges will be provided. Lab data collected during the post-treatment period will be flagged. Urinalysis will be presented in listings and will not be summarized

Liver function parameters

Liver function parameters of interest are total bilirubin (BILI), ALT, AST and alkaline phosphatase (ALP). The number and percentage of participants with worst post-baseline values as per Novartis Liver Toxicity guideline will be summarized. Because the study protocol inclusion criteria allowed participants to be enrolled with elevated baseline (BL) ALT or AST values, these are distinguished in the assessment.

The following summaries will be produced:

- Peak post-baseline values
  - ALT > 3×ULN
  - ALT > 5×ULN
  - ALT > 10×ULN
  - ALT > 20×ULN

- AST > 3×ULN
- AST > 5×ULN
- AST > 10×ULN
- AST > 20×ULN
- ALT or AST > 3×ULN
- ALT or AST > 5×ULN
- ALT or AST > 8×ULN
- ALT or AST > 10×ULN
- ALT or AST > 20×ULN
- BILI > 2×ULN
- BILI > 3×ULN

- Combined elevations post-baseline
  - AST and ALT ≤ ULN at baseline
    - (ALT or AST > 3×ULN) and BILI > 2×ULN
    - (ALT or AST > 3×ULN) and BILI > 2×ULN and ALP ≥ 2×ULN
    - (ALT or AST > 3×ULN) and BILI > 2×ULN and ALP < 2×ULN
  - ALT or AST > ULN at baseline
    - (Elevated ALT or AST) and BILI > 2×BL and BILI > 2×ULN
    - (Elevated ALT or AST) and BILI > 2×BL and BILI > 2×ULN and ALP ≥ 2×ULN
    - (Elevated ALT or AST) and BILI > 2×BL and BILI > 2×ULN and ALP < 2×ULN

Combined elevations post-baseline are based on the peak values at any post-baseline time for a participant.

(Elevated AST or ALT) is defined as:

- > 3×ULN if ≤ ULN at baseline, or
- (> 3× baseline or > 8×ULN) if > ULN at baseline

Potential Hy's Law events are defined as those participants who, depending on their baseline status, fulfill one of the criteria, i.e., (ALT or AST > 3 x baseline) OR (ALT or AST > 8.0 x ULN), whichever is lower, combined with (BILI > 2 x baseline AND > 2.0 x ULN). Further medical review has to be conducted to assess potential confounding factors such as liver metastases, liver function at baseline etc.

In addition, a listing of the hepatic laboratory values (BILI, ALT, AST and ALP) will be provided with values x.x times above ULN and CTCAE grades flagged. Peak total bilirubin vs peak ALT/AST values will also be graphically presented (eDISH plot). If any participants are identified as potential Hy's law cases, a graph with the time course of liver chemistry values and dose will be prepared per participant.

2.9.4 Other safety data

2.9.4.1 ECG and cardiac imaging data

12-lead ECGs including PR, QRS, QT and QTcF intervals and heart rate will be obtained for each participant during the study. ECG data will be read and interpreted centrally. The average of the ECG parameters at each assessment should be used in the analyses. ECGs collected during the on-treatment period will be summarized.

The number and percentage of participants with notable ECG values will be presented by treatment arm based on the categories below. ECG shift table based on notable values will also be presented by treatment arm.

- QT and QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60 ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline > 25% and to a value > 100 bpm
  - Decrease from baseline > 25% and to a value < 50 bpm
- PR
  - Increase from baseline > 25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline > 25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of all ECG assessments will be produced by cohort and notable abnormalities will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged. In addition, descriptive statistical analysis (mean and standard deviation) by time point of assessment for ΔQTcF (QTcF change from baseline) will be carried out.

Left ventricular ejection fraction (LVEF) data will be reported on the "Cardiac Imaging" eCRF. The worst decrease in LVEF from baseline will be calculated for each participant (by subtracting the baseline LVEF % from the LVEF % at each post-baseline assessment) and summarized. The summary will include the number and percentage of participants regardless of the method used in the following notable LVEF values:

- Absolute decrease from baseline ≥ 10% < 20% or LVEF ≥ 40% ≤ 50% (CTCAE grade 2)
- Absolute decrease from baseline ≥ 20% or LVEF ≥ 20% < 40% (CTCAE grade 3)
- Absolute LVEF < 20% (CTCAE grade 4)

LVEF shift table to compare baseline to the worst post-baseline on-treatment value (the lowest value corresponds to "worst") will also be presented.

Baseline categories is defined as follows:

- LVEF > 50%, LVEF ≥ 40% ≤ 50%, LVEF ≥ 20% < 40%, LVEF < 20%

Post-baseline categories correspond to CTCAE grade, defined as follows:

- LVEF > 50%,
- Absolute decrease from baseline ≥ 10% < 20% or LVEF ≥ 40% ≤ 50% (CTCAE grade 2)
- Absolute decrease from baseline ≥ 20% or LVEF ≥ 20% < 40% (CTCAE grade 3)
- LVEF < 20% (CTCAE grade 4)

A listing of all cardiac imaging data will be produced by cohort and notable abnormalities will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.9.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: systolic and diastolic blood pressure (mmHg), pulse (beats per minute), body temperature (°C), respiratory rate (breaths per minute, brpm), weight (kg), and height (cm).

Vital signs collected during the on-treatment period will be summarized. The number and percentage of participants with notable vital signs values will be presented based on the categories below.

Clinically notable elevated values:

- Systolic BP: ≥ 180 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 105 mmHg and an increase ≥ 15 mmHg from baseline
- Body temperature: ≥ 39.1°C
- Weight: an increase from baseline of ≥ 10%
- Pulse rate: ≥ 100 bpm with an increase from baseline of ≥ 25%
- Respiratory rate: ≥ 20 brpm with an increase from baseline of > 20%

Clinically notable values below the normal values:

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Weight: a decrease from baseline of ≥ 10%
- Pulse rate: ≤ 50 bpm with a decrease from baseline of ≥ 25%
- Respiratory rate: ≤ 8 brpm with a decrease from baseline of > 20%

A listing of all vital sign assessments will be produced, and notable values will be flagged. In the listing, the assessments collected during the post-treatment period will be flagged.

2.9.4.3 ECOG performance status

The performance status will be assessed according to the ECOG performance status scale as specified in Table 2-7 below, ranging from 0 (most active) to 5 (least active).

Table 2-8 ECOG performance status

Grade	ECOG 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

The rules and time windows defined in Section 2.1.3.9 will be used to group the ECOG PS data over time.

Frequency counts and percentages of participants in each score category will be provided by time point for the on-treatment period. Shift tables of ECOG performance status at baseline to worst post-baseline ECOG performance status by score will be provided by cohort using the safety set. ECOG performance status at each time point will be listed.

2.10 Analyses supporting secondary objectives – pharmacokinetic endpoints

To characterize the pharmacokinetics of JDQ443 is a secondary objective of the study. The PAS and FPAS will be used in pharmacokinetic data analysis and PK summary statistics. JDQ443 concentrations and PK parameters (as feasible) of non-Chinese, Chinese participants (subgroup 3) and all participants will be reported separately for each of the two cohorts.

PK concentrations

JDQ443 concentration data will be listed by cohort, participant, and visit/sampling time point using the PAS. Descriptive summary statistics will be provided by cohort and visit/sampling time point, including the frequency (n, %) of concentrations below the lower limit of quantification (anticipated LLOQ: 5 ng/mL).

Summary statistics will include n (number of participants with evaluable values), m (number of non-zero concentrations), mean (arithmetic and geometric), SD, coefficient of variation (CV; arithmetic and geometric), median, minimum, and maximum.

A graphical presentation will be provided on the mean concentration at each scheduled time point, when the full PK profile is available.

PK parameters

PK parameters such as listed in Table 2-8 will be derived using non-compartmental analysis using Phoenix WinNonlin (Version 8.0 or higher) and reported, if feasible.

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

Table 2-9 Non-compartmental pharmacokinetic parameters

AUC_{lastss}	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_{maxss}	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 steady-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)

Handling of PK data below LLOQ

All concentration values below the LLOQ are set to zero by the Bioanalyst and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing data for any PK data will not be imputed and will be treated as missing.

2.11 Analyses supporting secondary objectives – patient-reported outcomes

To assess the effect of JDQ443 on patient-reported lung cancer symptoms, health related quality of life, and health status, as well as the participants perception of overall side effects via patient-reported outcomes (PRO) questionnaires are secondary objectives of the study.

Data collected in the following patient-reported outcomes questionnaires up to the data cut-off date for the primary analysis will be analyzed by cohort (A and B): the NSCLC-SAQ and the EORTC QLQ-C30. The FAS will be used for analyzing PRO data. No multiplicity adjustment will be applied.

The NSCLC disease related symptoms as measured by the NSCLC-SAQ and physical function scale score of the QLQ-C30 are identified as the primary PRO variables of interest. Global health status (GHS) and role function scale scores of the QLQ-C30 is identified as secondary PRO variables of interest.

Scoring of PRO data and methods for handling of missing items or missing assessments will follow 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.

2.11.1 Time-to-event analyses

The physical function (PF) scale score of the QLQ-C30 questionnaire and the total score (TS) of the NSCLC-SAQ will be analyzed with regard to time to definitive deterioration (TTDD). TTDD analyses will be conducted using the data collected during the on-treatment period.

TTDD of the domains of interest is defined as the time from the date of enrollment to the date of meaningful worsening (defined below for each scale) from baseline with no later improvement above this threshold observed during the course of the treatment or until death due to any cause (withina period of time defined by 2 times the period between two assessments definded in section 2.1.3.9 plus twice the protocol defined PRO assessment interval(+/-3 days)). If a patient has not had an event prior to analysis cut-off date or the start of another anticancer therapy (with the exception of allowed radiotherapy), time to deterioration will be censored at the date of the last adequate PRO evaluation. Only assessments collected while the patient is in on-treatment period will be included in the PRO TTDD. Participants with no baseline data or no post-baseline data will be censored at the start of treatment, except if death happen within the period of time as mentioned above..

The distribution of TTDD will be summarized using the Kaplan-Meier method, and the Kaplan-Meier curves, medians (in months) and 95% confidence intervals of the medians will be presented. Censoring reasons for time to definitive deterioration will be summarized.

Thresholds of meaningful deterioration

- QLQ-C30, physical function scale
  - The first deterioration threshold is defined as a 10-point decrease from baseline (Coon et al 2022)
- NSCLC-SAQ
  - For the total score the deterioration threshold is 1 point

2.11.2 Change from baseline

Change from baseline in the observed scores at each scheduled assessment timepoint using the time windows described in Section 2.1.3.9 will be summarized for the following:

- NSCLC-SAQ total score, and each NSCLC-SAQ items/domains.
- EORTC QLQ-C30 all domains, subscales and items

Additionally, change from baseline at the time of each assessment will be plotted and summarized for the above variables.

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.

2.11.3 Other analyses

Descriptive statistics will be used to summarize the observed scores of the EORTC QLQ-C30 andNSCLC-SAQ, at each scheduled assessment timepoint using the time windows described in Section 2.1.3.9. All questionnaire data will be listed and those collected in the post-treatment period will be flagged in the listings.

The quality of completion of the PRO domain and total scores will be described for each scheduled assessment timepoint. In addition to the number and percentage of completed domain scores and the number and percentage of missing domain scores, the following categories of item-level missingness will be evaluated within each domain or measure:

- Number and percentage of participants who completed all questions
- Number and percentage of participants who completed the minimum requirement for scoring
- Number and percentage of participants who completed at least one question

The denominator for calculating percentages is the number of participants who remain in the study at each assessment.

Where available, the reasons for missing PRO data will be summarized. Additional analyses may be performed if deemed necessary. Such analyses will be defined in a separate PRO SAP.

[redacted]

2.15 Interim analysis

The planned interim analyses for futility will be performed separately for each of the two cohorts. A separate interim analysis plan will provide details and specifications for the analyses.

2.15.1 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 treatment 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 ≥ [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 calculati the interim analysis.

The cohort will be stopped for futility at the interim analysis if the observed ORR is ≤ [redacted] corresponding to 9 or less responders (at least [redacted] 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 [redacted]

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

Table 2-10 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	[redacted]
6	
7	
8	
9	
10	

Responders at IA out of 30 evaluable participants	Predictive probability of success (%)
11	[redacted]
12	

2.15.2 Key secondary endpoint: ORR in cohort B

One interim analysis is planned for cohort B based on approximately the first [redacted] 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 20% will be used, i.e., the prior distribution will be Beta (0.25, 1) 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 2-10 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 enrollment will continue after the interim analysis.

Table 2-11 PPoS at the final analysis based on various numbers of responders observed

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

3 Sample size calculation

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).

3.1 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 2.6.

The exact 95% CIs for various sample sizes and potential observed ORRs are shown in Table 3-1.

Table 3-1 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 (%)
[redacted]			

The operating characteristics (for 90 participants) are shown in Table 3-2. The table presents the probability of stopping at the interim analysis, 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 3-2 Operating Characteristics (cohort A)

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

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

*Assuming IA at 30 evaluable participants

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

The calculations were made using the software R.

3.2 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 2.7.

The exact 95% CIs for various sample sizes and observed ORRs are shown in Table 3-3.

Table 3-3 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 (%)
[redacted]			

The operating characteristics (for 30 participants) are shown in Table 3-4. The table presents the probability of stopping at the interim analysis, 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 3-4 Operating characteristics (cohort B)

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

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

*[redacted]

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

The calculations were made using the software R.

4 Appendix

4.1 Imputation rules

4.1.1 Study drug

Complete dates are required per eCRF. For exceptional cases where a missing or partial date remains after data cleaning, the following rules should be used for the imputation of the dose end date of the study treatment:

Scenario 1

If the dose end date is completely missing and there is no end of treatment (EOT) and no death date, the participant is considered as ongoing. The participant should be treated as ongoing, and the cut-off date should be used as the last dosing date.

Scenario 2

If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing and the EOT completion date is complete, then this latter date should be used.

Case 2: Only year (YYYY) of the dose end date is available and YYYY < the year of EOT date, then use 31DECYYYY.

Case 3: Only year (YYYY) of the dose end date is available and YYYY = the year of EOT date, then use EOT date.

Case 4: Both year (YYYY) and month (MMM) are available for dose end date and YYYY = the year of EOT date and MMM < the month of EOT date, then use last day of the Month (MMM).

Case 5: Both year (YYYY) and month (MMM) are available for dose end date and YYYY = the year of EOT date and MMM = the month of EOT date, then use EOT date.

All other cases should be considered as a data issue and the data manager of the study should be contacted.

After imputation, compare the imputed date with start date of treatment.

- If the imputed date is < start date of treatment, then use the treatment start date
- Otherwise, use the imputed date

Participants with missing start dates are to be considered missing for all study treatment related calculations and no imputation will be made. If the start date is missing, then the end-date should not be imputed.

4.1.2 AE, concomitant medication (CM), and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (lab, ECG, vital signs)

Missing element	Rule
day, month, and year	No imputation will be done for completely missing dates
day, month	If available year = year of study treatment start date, then If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JANYYYY, Else set start date = study treatment start date. If available year > year of study treatment start date, then 01JANYYYY. If available year < year of study treatment start date, then 01JULYYYY.
day	If available month and year = month and year of study treatment start date, then If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY, Else set start date = study treatment start date. If available month and year > month and year of study treatment start date, then 01MONYYYY. If available month and year < month year of study treatment start date, then 15MONYYYY.

Table 5-2 Imputation of end dates (AE, CM)

Missing element	Rule
day, month, and year	Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*.
day, month	If a partial end date contains the year only, set end date = earliest of (31DECYYYY, end date of the on-treatment period*).
day	If a partial end date contains the month and year, set end date = earliest of (last day of the month, end date of the on-treatment period*).

*= last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date)

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

4.1.3 Prior ANP, concomitant ANP, non-drug therapy, and diagnosis date imputation

Table 5-3 Imputation of end dates (prior ANP, concomitant ANP, non-drug therapy, diagnosis)

Missing date Scope	Missing element	Rule
Post-treatment anti-neoplastic therapy (including radiotherapy/medication/surgery) start date	Day, month	Imputed date = max (last date of study treatment + 1, 01JAN).
	Day	Imputed date=max (last date of study treatment + 1, first day of the month).
Post-treatment anti-neoplastic therapy (including radiotherapy/medication/surgery) end date	All scenarios	No imputation
Prior anti-neoplastic surgery start date	Day, month	If available year = year of treatment start date, then set start date = treatment start date, else set start date = 01JULYYYY.
	Day	If available month and year = month and year of treatment start date, then set start date = study treatment start date, else set start date = 15MONYYYY.
Prior anti-neoplastic surgery start date	All scenarios	No imputation
Prior anti-neoplastic therapy – medication, date of progression	Day	Set to max (start date of prior antineoplastic therapy, 1st day of the month), if day is missing
	Day, month	No imputation
Non-drug therapy start date	Day and month (same as CM)	If available year = year of study treatment start date, then if stop date contains a full date and stop date is earlier than study treatment start date, set start date = 01JANYYYY, else set start date = study treatment start date. If available year > year of study treatment start date, then set start date = 01JANYYYY. If available year < year of study treatment start date, then set start date = 01JULYYYY.
	Month	If available year = year of study treatment start date, then

Missing date Scope	Missing element	Rule
		if stop date contains a full date and stop date is earlier than study treatment start date, then set start date= DDJANYYYY, else set start date = study treatment start date. If available year > year of study treatment start date, then set start date = DDJANYYYY. If available year < year of study treatment start date, then set start date = DDJULYYYY.
	Day (same as CM)	If available month and year = month and year of study treatment start date, then If stop date contains a full date and stop date is earlier than study treatment start date, then set start date = 01MONYYYY, else set start date = study treatment start date. If available month and year > month and year of study treatment start date, then set start date = 01MONYYYY. If available month and year < month year of study treatment start date, then set start date = 15MONYYYY.
Date of Initial Diagnosis (of cancer), date of most recent recurrence*	Day and month	Set to 01JANYYYY.
	Day	Set to 01MONYYYY.

* If because of this imputation the chronology of the events is altered, then the imputation should be made to the minimum value up to where the chronology remains unchanged. E.g., if due to imputation the date of most recent recurrence becomes prior to the initial diagnosis date then it should be set to initial diagnosis date.

4.1.4 Other imputations

Incomplete assessment dates for tumor assessment

All investigation dates (e.g., MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g., MRI scan, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/NE. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation. 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 the previous and the following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Incomplete death date or last known participant alive date from survival eCRF page

For rare cases when either day is missing or both month and day are missing for the date of death, the following partial imputation rules will be implemented:

- If only day is missing, then impute the last known participant alive date (from "Survival" eCRF) or death date with max[(01MONYYYY), any valid date used for deriving last contact date + 1].
- If both day and month are missing, then impute the last known participant alive date or death date with max[01JANYYYY, any valid date used for deriving last contact date + 1].

4.2 AEs coding/grading

AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) using the latest version available prior to clinical database lock and will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

4.3 Laboratory parameters derivations

Grade categorization of lab 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. The criteria to assign CTCAE grades are given in a Novartis internal document for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE version 5.0, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

4.3.1 Grading imputation rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as "< X" (i.e. below limit of detection) or "> X", prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a certain differential, "xxx"

xxx count = (WBC count) × (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) − 0.8 [Albumin (g/dL) − 4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL (by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL (by dividing by 0.2495). For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

4.4 Statistical models

4.4.1 Analysis supporting primary objective(s)

Confidence interval for overall response rate and disease control rate

Responses will be summarized in terms of percentage rates with a 100(1 − α)% confidence interval using an exact binomial approach (implemented using SAS procedure FREQ with EXACT statement for one-way tables (Clopper, Pearson 1934).

4.4.2 Analysis supporting secondary objective(s)

Kaplan-Meier estimates

For time-to-event endpoints (DOR, PFS, OS), an estimate of the survival function will be constructed using the Kaplan-Meier (product-limit) method as implemented in SAS PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

Median survival will be obtained along with the 95% confidence interval calculated from PROC LIFETEST output using the method of (Brookmeyer, Crowley 1982). Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula (Collett 1994).

4.5 Determination of missing adequate assessments

The term "missing adequate tumor assessment" is defined as a tumor assessment not done or a tumor assessment with overall lesion response "NE". For the sake of simplicity, a "missing adequate tumor assessment" will also be referred to as a "missing assessment".

As described in Appendix 8 (Section 10.8) of the clinical study protocol, the PFS censoring and event date options depend on the presence and the number of missing tumor assessments (TAs). In the analysis of PFS, an event occurring after two or more missing assessments is censored at the last adequate tumor assessment, i.e. the last assessment preceding the missing assessment(s).

An exact rule to determine whether there is no, one or two missing TAs is therefore needed. This rule is based:

- On the time interval between the last adequate tumor assessment (LATA) date and the event date
- On the time interval between the last adequate tumor assessment date and the cut-off date

In this study, the protocol defined schedule of assessments is

- Every 6 weeks during the first 54 weeks (i.e. at week 6, 12, 18, 24, 30, 36, 42, 48, 54)
- Every 12 weeks thereafter (i.e. at weeks 66, 78, 90, etc.) until confirmed PD

The scheduled date of tumor assessments (in weeks from start of treatment), protocol-specified windows for tumor assessments (± 7 days/1 week), and the thresholds for LATA to belong to a visit can be found in the following Table 5-4.

Table 5-4 Schedule for tumor assessment and time windows

Assessment schedule		Scheduled date − 1 week	Scheduled date (weeks from start of treatment)	Scheduled date + 1 week	Threshold (weeks)*
Every 6 weeks for the first 54 weeks	Baseline	0	0#	1	N/A
	C3D1	5	6	7	9
	C5D1	11	12	13	15
	C7D1	17	18	19	21
	C9D1	23	24	25	27
	C11D1	29	30	31	33
	C13D1	35	36	37	39
	C15D1	41	42	43	45
	C17D1	47	48	49	51
	C19D1	53	54	55	60
Every 12 weeks thereafter	C23D1	65	66	67	72
	C27D1	77	78	79	...
	…				

* The threshold corresponds to the mid-point between the current and next visit (except for baseline) and to the upper limit for LATA to be matched to a certain scheduled assessment. e.g. if LATA is at week 10, this is after threshold for C3D1 and before that for C5D1, so the matching scheduled assessment is C5D1.

Day of start of treatment is taken as 0.

To calculate the number of missing tumor assessments, the LATA before an event is matched with a scheduled tumor assessment using the time window in the table above (essentially whichever scheduled assessment it is closest to).

D1 and D2 are calculated for that scheduled assessment based on the protocol-specified schedule and windows.

- The threshold D1 is defined as the protocol-specified time interval between the TAs plus 2× the protocol-allowed time window around the assessments (i.e. = 2×1 week = 2 weeks).
- The threshold D2 is defined as twice the protocol-specified time interval between the TAs plus 2× the protocol-allowed time window around the assessments (except when the matched scheduled tumor assessment is from C15D1 to C19D1 in which case D2 is defined in Rule 2).

Since there is a change of schedule for tumor assessments after first 54 weeks, D1 and D2 are defined differently depending on when LATA occurs:

- Rule 1: if LATA happens within 45 weeks of start of treatment, the matched scheduled tumor assessment is C15D1, D1 = 6+2 = 8 weeks and D2 = 6×2+2 = 14 weeks.
- Rule 2: if LATA happens after 45 weeks from start of treatment, the matched scheduled tumor assessment is C15D1 or after, but within 51 weeks (the matched scheduled tumor assessment is C17D1), D1 = 6+2 = 8 weeks and D2 = 6+12+2 = 20 weeks.
- Rule 3: if LATA happens after 51 weeks from start of treatment (the matched scheduled tumor assessment is C17D1), D1 = 12+2 = 14 weeks and D2 = 12×2+2 = 26 weeks.

The number of missing events is defined as:

- An event after LATA+D1 weeks will be considered as having ≥ 1 missing assessment
- An event after LATA+D2 weeks will be considered as having ≥ 2 missing assessments

The same definition of D2 will be used to determine the PFS censoring reason. If there is no post-baseline adequate tumor assessment available (before an event or a censoring reason occurred), the start of treatment date will be used to compute the interval.

If the time interval between the LATA date and the earliest of the following dates:

- Analysis cut-off date
- Date of consent withdrawal
- Date of start of new anticancer therapy
- Date of study treatment discontinuation due to lost to follow-up or date of end of post-treatment efficacy follow-up discontinuation due to lost to follow-up

is less or equal to D2, then the PFS censoring reason will be respectively:

- Ongoing without event
- Withdrew consent
- New anticancer therapy given prior to protocol defined progression
- Lost to follow-up

However, if the time interval is larger than D2 with no event, then the PFS censoring reason will always default to “Adequate assessment no longer available”. If the time interval between the last adequate tumor assessment date and the PFS event date is larger than D2, then the participant will be censored, and the censoring reason will be “Event documented after two or more missing tumor assessments”.

No baseline tumor assessment

Since the timing of disease progression cannot be determined for participants with missing baseline tumor assessment, these participants are censored in the PFS analysis at the date of start of treatment. This only applies to the "progressive disease" component of the PFS assessment. Participants without any baseline tumor assessment who die within the D2 time interval from the date of start of treatment will be counted as having an event in at the date of death.

4.6 Patient reported outcomes

The text below gives more detailed instructions and rules needed for programming of the analyses described in Section 2.11.

4.6.1 NSCLC-SAQ

The NSCLC-SAQ consists of seven items covering five domains:

- Cough
- Pain (2 items)
- Dyspnea
- Fatigue (2 items)
- Appetite

Items 1, 2 and 3 assess intensity and have response options of No <symptom> at all, Mild <symptom>, Moderate <symptom>, Severe <symptom>, and Very Severe <symptom>. Items 4 through 7 assess frequency and have response options of Never, Rarely, Sometimes, Often, and Always. The responses are coded as 0, 1, 2, 3, 4, where 0 corresponds to the lowest severity (no, never) and 4 corresponds to the highest (very severe, always).

The scoring algorithm of the NSCLC-SAQ total score is as follows:

- Cough score: score of the cough item, or missing if skipped
- Fatigue score: if both items present, compute mean; or use score from 1 item if the other is missing; or set to missing if both are skipped
- Pain score: if both items present, use most severe of both; or use score from 1 item if the other is missing; or set to missing if both are skipped
- Dyspnea score: score of the shortness of breath item, or missing if skipped
- Appetite score: score of the poor appetite item, or missing if skipped
- Total score: sum all five domain scores; if any are missing, a total score is not computed. This creates a total score ranging between 0 and 20 with higher scores indicating more severe symptomatology

4.6.2 EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire contains 30 items and is composed of both multi-item scales and single-item measures. These include

- Five functional scales (physical, role, emotional, cognitive and social functioning),

- Three symptom scales (fatigue, nausea/vomiting, and pain),
- A global health status / QoL scale, and
- Six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact).

All 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 high/healthy level of functioning; a high score for the global health status represents a high quality of life, but a high score for a symptom scale represents a high level of symptomatology/problems. Note: This difference needs to be considered in the review and interpretation of the outputs.

QLQ-C30 scale scores will be generated by first obtaining the raw scores by averaging the item responses on the questions which contribute to the scale. Then a linear transformation will be used to standardize the raw score so that scores range from 0 to 100. This transformation is specified in the scoring manual provided by the developers. Scores in each scale will be generated if at least half of the items comprising the scale have been answered. For single item scales with missing responses and scales where less than half of the items have not been answered, scale scores will be set to missing.

[redacted]

[redacted]

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