Summary Table of Study Protocol

Title	Matching-adjusted indirect treatment comparison of sotorasib vs adagrasib for previously treated non-small cell lung cancer with *KRAS* G12C mutation
Protocol Version Identifier	20240246
Date of Last Version of the Protocol	07 November 2024
Therapeutic Area	Oncology
Reference Systematic Literature Review Protocol Title and Number	Systematic review of prevalence of *KRAS* mutations, co-mutations and associated clinical outcomes among patients with non-small cell lung cancer (NSCLC) or colorectal cancer (CRC) (Amgen Study Number 20190344, updated July 2022) A systematic literature review (SLR) of randomized controlled trials (RCTs) to evaluate the comparative effectiveness and safety of second-line systemic therapies for treatment in adults with advanced or metastatic non-small cell lung cancer (NSCLC) (Amgen Study Number 20200340, updated July 2022)
Research Question and Objectives	Research question: What is the relative efficacy and safety of sotorasib vs adagrasib for previously treated non-small cell lung cancer with *KRAS* G12C mutation? Objective: 1) To estimate the treatment efficacy of sotorasib relative to adagrasib for previously treated non-small cell lung cancer with *KRAS* G12C mutation 2) To estimate the safety of sotorasib relative to adagrasib for previously treated non-small cell lung cancer with *KRAS* G12C mutation
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STUDY GLOSSARY

Term	Definition
Bias	Systematic error.
Cohort	Group of individuals characterized by a common experience (eg, occurrence of a specified disease; exposure to a given medication).
Confounder	An extraneous factor that accounts for a difference in disease frequency between the exposure groups. Factors associated with these extraneous causal factors that can serve as surrogates for these factors also are commonly called confounders.
Effect-measure modifier	If an effect measure varies within categories or levels of a variable, that variable is described as an effect-measure modifier.
Evidence synthesis (ES)	Techniques comprising the pooling and analysis of data from different studies (eg, meta-analysis, network/meta-analysis). The studies from which data is combined can differ in relation to their design types, outcome measures, study interventions, study parameters, or patient population.
Exposure	Variable whose effect is of interest and is being studied.
Outcome	Event (such as disease occurrence or death) that is studied in relation to an exposure.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BRAF	B-Raf proto-oncogene, serine/threonine kinase
CNS	Central nervous system
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth receptor factor
ESS	Effective sample size
FDA	Food and Drug Administration
G12C	Codon 12 glycine to cysteine substitution
HR	Hazard ratio
IO	Immunotherapy
IPD	Individual patient level data
ITT	Intention-to-treat
KM	Kaplan–Meier
MAIC	Matching-adjusted indirect treatment comparison
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand-1
PFS	Progression-free survival
PICOS	Population, intervention, comparator, outcomes, and study design
RCT	Randomized controlled trial
ROS-1	C-ros oncogene 1
SAE	Serious adverse event
SLR	Systematic literature review
SMD	Standardized mean difference
STC	Simulated treatment comparison
TRAE	Treatment-related adverse event

2. ABSTRACT

- Study Title

  Matching-adjusted indirect treatment comparison of sotorasib vs adagrasib for previously treated non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation

- Relevant Systematic Literature Review (SLR)

  Two SLRs [1, 2] were conducted to identify evidence on efficacy and safety outcomes for patients with *KRAS* G12C-mutated NSCLC. The SLRs originally identified two phase 2 single arm trials, CodeBreaK 100 [3] for sotorasib and KRYSTAL-1 [4] for adagrasib, which were evaluated in an MAIC conducted previously (20220180) [5]. The results of the phase 3 randomized controlled trials (RCTs) for sotorasib in CodeBreaK 200 and adagrasib in KRYSTAL-12 [6], were not available at the time of the SLRs but were published recently. Nonetheless, as the only two U.S. Food and Drug Administration (FDA)/ European Medicines Agency (EMA) approved inhibitors of $KRAS^{G12C}$, the phase 3 RCTs for sotorasib and adagrasib will be considered in this indirect treatment comparison.

- Research Question

  What is the relative efficacy and safety of sotorasib vs adagrasib for previously treated non-small cell lung cancer with *KRAS* G12C mutation?

- Background and Rationale

  As of August 2024, sotorasib and adagrasib are the only FDA/EMA approved $KRAS^{G12C}$ inhibitors for the treatment of NSCLC harboring a *KRAS* G12C mutation. In the absence of head-to-head clinical trials between sotorasib and adagrasib, a matching-adjusted indirect treatment comparison (MAIC) [5] based on the corresponding phase 2 single-arm trials, CodeBreaK 100 [3] and KRYSTAL-1 [4], was conducted to assess the relative efficacy of sotorasib vs adagrasib.

  With the availability of phase 3 RCT data for both drugs, the current MAIC aims to assess the relative efficacy and safety of sotorasib vs adagrasib using CodeBreaK 200 [7] and KRYSTAL-12 [6]. The purpose of this study is to provide a more recent update on the comparative efficacy and safety of the two drugs, which will in particular be needed in the discussion with payers.

- Feasibility

  A feasibility assessment of the indirect comparison between sotorasib (CodeBreaK 200) and adagrasib (KRYSTAL-12) was undertaken. It was concluded

that CodeBreaK 200 and KRYSTAL-12 share similar methodological and clinical similarities in terms of study design, eligibility criteria, primary and secondary endpoints, and baseline characteristics with the possibility of adjusting for imbalanced ones (Section 8.1). Therefore, these two trials are appropriate to be used for the indirect comparison of sotorasib and adagrasib. With the availability of individual patient level data (IPD) for the phase 3 RCT CodeBreaK 200 and aggregate data from the phase 3 RCT KRYSTAL-12, an MAIC analysis is proposed to assess the relative efficacy and safety of sotorasib vs adagrasib.

Due to early dropout, crossover and protocol deviations in both CodeBreaK 200 [8] and KRYSTAL-12, the comparator arm of the two trials were prone to significant bias. The magnitude of bias in the comparator arm of CodeBreaK 200 and KRYSTAL-12 appears to be different. The early dropout rate in the docetaxel arm of CodeBreaK 200 was 65% higher compared to the early dropout rate in the docetaxel arm in KRYSTAL-12. Furthermore, due to changes in the study design while the trial was already ongoing, there was significant informative censoring and crossover outside of the protocol in CodeBreaK 200. Informative censoring occurred, when patients progressed due to investigator assessment and subsequent confirmation-of-progression while not yet having progressed as per BICR. This is expected to overestimate PFS of docetaxel in CodeBreaK 200. Out-of-protocol crossover resulted in subjects taking sotorasib while being in the comparator arm which potentially affected PFS assessment. Significant bias in the docetaxel arm was acknowledged by regulatory bodies and resulted in not accepting CodeBreaK 200 as a confirmatory trial. Furthermore, despite being present in the comparator arm, this bias did not occur in the sotorasib or adagrasib arm from CodeBreak 200 and KRYSTAL-12 trials, respectively. Given these limitations, an unanchored MAIC that compares sotorasib arm and adagrasib arm will be conducted as the primary analysis. An anchored MAIC that uses docetaxel arm as the anchor will be conducted as a sensitivity analysis.

- Objectives

  The two main objectives of the current study are:

1) To estimate the treatment efficacy of sotorasib relative to adagrasib for previously treated non-small cell lung cancer with *KRAS* G12C mutation.
2) To estimate the safety of sotorasib relative to adagrasib for previously treated non-small cell lung cancer with *KRAS* G12C mutation

- Statistical Outcomes
  The analyses of this study will provide measures of relative treatment effect between sotorasib and adagrasib. Hazard ratios (HR) will be used to estimate the relative efficacy of sotorasib vs adagrasib for PFS, and odds ratios (OR) will be used for ORR and AEs.

- Statistical Analysis Plan
  Patient-level baseline characteristics and outcomes data for *KRAS* G12C NSCLC patients treated with sotorasib from the CodeBreaK 200 trial will be used. Given the lack of IPD for adagrasib, aggregated baseline patient characteristics will be used from the KRYSTAL-12 trial; Kaplan–Meier (KM) PFS curves will be digitized and used to simulate pseudo patient-level data using the algorithm of Guyot 2012 [9]. For base-case analysis, an unanchored MAIC will be conducted using the method described by Phillippo 2018 [10]. Covariates identified as prognostic variables and/or effect modifiers for prognosis in NSCLC by clinical experts and literature will be used to adjust for the observed heterogeneity across studies. Survival outcomes will be analyzed using weighted Cox regression, and binary outcomes will be analyzed using weighted logistic regression. Robust variance estimator will be used to estimate confidence intervals.

  Sensitivity analyses will be conducted by including additional covariates to assess the robustness of results, as well as using an anchored MAIC approach. Subgroup analyses will be conducted for patients with brain metastases.

3. AMENDMENTS AND UPDATES

None.

4. OBJECTIVES

Using data from the CodeBreaK 200 [7] and KRYSTAL-12 [6], the objectives of this study are:

1) To estimate the treatment efficacy of sotorasib relative to adagrasib for previously treated non-small cell lung cancer with *KRAS* G12C mutation
2) To estimate the safety of sotorasib relative to adagrasib for previously treated non-small cell lung cancer with *KRAS* G12C mutation

5. OUTCOMES

In line with the objectives, the outcomes to be assessed in the MAIC are PFS, ORR, and AEs of interest. OS for KRYSTAL-12 was not yet reported, therefore it was not possible to be included as an outcome. The analyses will provide measures of relative treatment effect such as HRs and ORs to estimate the comparative efficacy and safety of sotorasib vs adagrasib in the treatment of previously treated locally advanced or metastatic NSCLC with *KRAS* G12C mutation.

6. BACKGROUND AND RATIONALE

6.1 Rationale and Feasibility

Sotorasib is a small molecule that selectively targets the *KRAS* codon 12 glycine to cysteine substitution (G12C) mutation to treat adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation. Sotorasib has been evaluated for safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy in the treatment of locally advanced or metastatic *KRAS* G12C-mutated NSCLC in the phase 1/2, single-arm, open-label trial – CodeBreaK 100 (Amgen study number 20170543, NCT03600883) [3], and in the phase 3, randomized, open-label trial – CodeBreaK 200 (Amgen study number 20190009, NCT04303780) [7]. In May 2021, FDA granted accelerated approval to sotorasib, for adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy [11]. CodeBreaK 200 demonstrated improved PFS and a more favorable safety profile of sotorasib over docetaxel, in patients with previously treated advanced NSCLC with the *KRAS* G12C mutation who progressed after previous platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor. However, due to informative censoring attributed to early dropout and out-of-protocol crossover among patients receiving docetaxel, the comparator arm of CodeBreaK 200 was prone to significant bias [8], which was acknowledged by FDA and resulted in FDA and EMA not accepting CodeBreaK 200 as a confirmatory trial.

A second small molecule inhibitor of $KRAS^{G12C}$, adagrasib, has demonstrated clinical efficacy in a phase 1/2, single-arm, open-label trial – KRYSTAL-1 (NCT03785249) [4], and recently in a phase 3, randomized, open-label trial – KRYSTAL-12 (NCT04685135) [6]. KRYSTAL-12 demonstrated improved PFS of adagrasib over docetaxel, in patients with previously treated advanced NSCLC with the *KRAS* G12C mutation. In December 2022, the FDA granted accelerated approval to adagrasib, for adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy [12].

In the absence of a head-to-head trial comparing sotorasib and adagrasib, an MAIC was conducted in April 2023 to assess the relative efficacy of sotorasib vs adagrasib using the phase 2 single-arm trials CodeBreaK 100 and KRYSTAL-1. Results showed no significant differences between sotorasib and adagrasib in terms of PFS, OS and ORR [5]. At the time this MAIC analysis was conducted, results from phase 3 CodeBreaK 200 and KRYSTAL-12 trials were not available.

For the current MAIC analysis, IPD are available for CodeBreaK 200 with a data cutoff date of 2 Aug 2022 (primary analysis). The primary outcome in CodeBreaK 200 was PFS, and secondary outcomes included OS, ORR, and AEs. Results for KRYSTAL-12 have been presented at the 2024 ASCO Annual Meeting and 2024 ESMO congress [6, 13] with the primary endpoint PFS and secondary endpoint ORR and AEs reported; OS data were immature at the data cutoff (31 December 2023). The availability of IPD for CodeBreaK 200 and aggregate data for KRYSTAL-12 presents an opportunity to conduct an indirect treatment comparison using the two phase 3 RCTs for the outcomes of interest.

Two methods for estimating comparative efficacy and safety, MAIC and simulated treatment comparison (STC), have been widely used for indirect comparisons. MAIC is considered the appropriate method for this study which has few comparators and multiple outcomes, whereas STC is better suited for scenarios with multiple comparators and fewer outcomes [14, 15]. Additionally, for non-linear outcomes, such as time to event, it is recommended to use MAIC over STC. MAICs are increasingly being used in oncology studies, and act as reliable tools to provide useful insights to clinicians and payers regarding the value of new treatments. Several MAICs have previously been conducted in NSCLC [16-19].

6.2 Disease or Therapeutic Area

Globally, lung cancer is one of the most commonly diagnosed cancer types (11.4% of total cases) and the leading cause of cancer-related death (18.0% of total cancer deaths) [20]. NSCLC is the most common form, comprising 80-85% of all lung cancer [21] and is a molecularly heterogeneous disease with poor prognosis [22]. The three human *RAS* genes (*KRAS*, *NRAS*, and *HRAS*) are the most frequently mutated oncogenes in human cancer. *KRAS* (Kirsten rat sarcoma viral oncogene homolog) is the isoform most prevalently mutated in lung cancers [23].

Sotorasib and adagrasib are the only two FDA/EMA-approved inhibitors of $KRAS^{G12C}$ for the treatment in adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy [11, 12]. The approvals of sotorasib and adagrasib were based on the phase 2 single-arm trials CodeBreaK 100 and KRYSTAL-1, respectively. Following the phase 2 trials, the phase 3 RCT of sotorasib, CodeBreaK 200, demonstrated improved PFS and a more favorable safety profile of sotorasib over docetaxel [7]. The phase 3 RCT of adagrasib, KRYSTAL-12, showed improved PFS of adagrasib over docetaxel [6].

6.3 Scope for Analysis

The scope of the analysis includes obtaining estimates of relative treatment effects (PFS, ORR, AEs) for the comparison of sotorasib vs adagrasib in treatment of patients with previously treated advanced NSCLC with the *KRAS* G12C mutation.

To identify all available evidence for the clinical efficacy and safety of treatments administered following progression on at least one prior therapy for adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC, two SLRs had been conducted; details of the methodology (methods for data collection, data abstraction, quality assessment and descriptive analysis) are described in the respective protocols [1, 2]:

- *Systematic review of prevalence of KRAS mutations, co-mutations and associated clinical outcomes among patients with non-small cell lung cancer (NSCLC) or colorectal cancer (CRC) (Amgen Study Number 20190344) – updated July 2022*
- *A systematic literature review (SLR) of randomized controlled trials (RCTs) to evaluate the comparative effectiveness and safety of second-line systemic therapies for treatment in adults with advanced or metastatic non-small cell lung cancer (NSCLC) (Amgen Study Number 20200340) – updated July 2022*

7. METHODS FOR DATA COLLECTION

7.1 Study Eligibility

The SLRs (Amgen Study Number 20190344 and 20200340) identified two phase 2 single arm trials, CodeBreaK 100 [3] for sotorasib and KRYSTAL-1 [4] for adagrasib. The results of the corresponding phase 3 RCTs for sotorasib (CodeBreaK 200) [7] and adagrasib (KRYSTAL-12) [6], were not available at the time of the SLRs but have been published recently.

Although there are other $KRAS^{G12C}$ inhibitors in development, none of them have FDA or EMA regulatory approvals. Therefore, it is determined that adagrasib is the only relevant comparator to sotorasib for the MAIC. The current study focuses on phase 3 RCTs. Both CodeBreaK 200 and KRYSTAL-12 met the eligibility criteria of the current study using the population, intervention, comparator, outcomes, and study design (PICOS) framework (Table 1). A detailed feasibility assessment of conducting an MAIC using CodeBreaK 200 and KRYSTAL-12 is described in Section 8.1.

Table 1. PICOS criteria for MAIC evidence base

PICOS Criteria	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥ 18 years) with locally advanced or metastatic *KRAS* G12C-mutated NSCLC who had received at least 1 prior systemic therapy	No *KRAS* G12C subgroup or population
Interventions	• Sotorasib • Adagrasib	Studies not evaluating an intervention of interest
Comparators	Studies that contain one of the interventions of interest in at least one study arm	Studies not containing at least one comparator of interest
Outcomes	Studies reporting at least one outcome of interest as a primary or secondary endpoint: • Progression-free survival • Overall survival • Overall response rate • Adverse events	Studies not reporting on at least one of the outcomes of interest
Study design	Randomized controlled trial	N/A

Abbreviations: G12C, codon 12 glycine to cysteine substitution; NSCLC, non-small cell lung cancer

7.2 Patient-level Data

IPD from CodeBreaK 200 [7] and aggregate data (baseline patient characteristics, number of patients with event, and KM curves) from the KRYSTAL-12 [6] will be utilized.

7.3 Data Management and Quality Control Procedures

Data for CodeBreaK 200 will be stored in a secure environment, with access to the data through a secure connection to the Citrix platform. Data management and analyses will

be conducted using R version 4.3.1 within the R Studio environment [24]. The quality control of the R codes and reports will be conducted by a Cytel consultant who was not involved in developing the models and analysis outputs.

8. DATA SYNTHESIS AND STATISTICAL ANALYSIS

8.1 Summarize Individual Studies

An overview of the study characteristics for CodeBreaK 200 and KRYSTAL-12 are summarized in Table 2. Both trials had a randomized open-label design with similar inclusion and exclusion criteria, recruiting patients from multiple countries in Asia, Europe, America and Oceania. The two trials had a common comparator arm, docetaxel 75 mg/m² intravenously every 3 weeks. Both trials allowed crossover from the comparator arm to the intervention arm after disease progression, with 46 of 174 patients crossed over from docetaxel to sotorasib in CodeBreaK 200, and 44 of 152 patients crossed over from docetaxel to adagrasib in KRYSTAL-12.

Table 2. Study characteristics of CodeBreaK 200 and KRYSTAL-12

Study name	CodeBreaK 200	KRYSTAL-12*
Author, year	de Langen, 2023	Mok, 2024; Barlesi, 2024
Trial registry	NCT04303780	NCT04685135
Study design	Randomized, open-label, phase 3	Randomized, open-label, phase 3
Country	Australia, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Greece, Hungary, Italy, Japan, Republic of Korea, Netherlands, Poland, Portugal, Russian Federation, Spain, Sweden, Switzerland, United Kingdom, United States	Australia, Austria, Belgium, Czechia, France, Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Republic of Korea, Netherlands, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Singapore, Spain, Switzerland, United Kingdom, United States
Inclusion criteria	• Age ≥ 18 • Histologically or cytologically documented, locally advanced and unresectable or metastatic NSCLC, with the *KRAS* G12C mutation confirmed via central laboratory testing • Disease progression after previous platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor • ECOG PS of 0-1 • Have measurable disease according to Response Evaluation Criteria in Solid Tumors • Patients with treated, stable brain metastases were eligible	• Age ≥ 18 • Locally advanced or metastatic NSCLC with *KRAS* G12C mutation • Prior treatment with platinum-based chemotherapy and anti-PD-(L)1 therapy • ECOG PS of 0-1 • Treated, neurologically stable brain metastases allowed
Exclusion criteria	• New or progressing untreated brain lesions and/or symptomatic brain lesions • Previously identified oncogenic driver	• Prior treatment with an agent targeting $KRAS^{G12C}$ (e.g., sotorasib) • Active brain metastases

Study name	CodeBreaK 200	KRYSTAL-12*
	mutation other than *KRAS* G12C for which an approved therapy is available (e.g., EGFR, ALK, etc) • Previous treatment with docetaxel (neoadjuvant or adjuvant docetaxel was allowed if the tumor did not progress within 6 months of end of therapy) • Previous treatment with a direct $KRAS^{G12C}$ inhibitor • Systemic anticancer therapy within 28 days of study day 1 • Radiation therapy within 2 weeks of treatment initiation	
Intervention	Sotorasib: 960 mg orally once daily Docetaxel: 75 mg/m² intravenously every 3 weeks	Adagrasib: 600 mg orally twice daily Docetaxel: 75 mg/m² intravenously every 3 weeks
ITT population	Sotorasib: 171 Docetaxel: 174	Adagrasib: 301 Docetaxel: 152
Never receive assigned treatment	Sotorasib: 2 Docetaxel: 23	Adagrasib: 3 Docetaxel: 12
Cross over to intervention arm	Docetaxel to sotorasib: 46	Docetaxel to adagrasib: 44

* Country and exclusion criteria information for KRYSTAL-12 was obtained from ClinicalTrials.gov

Abbreviations: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth receptor factor; ITT, intention-to-treat; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand-1

Patient characteristics were compared between intervention arms for adagrasib (KRYSTAL-12) vs sotorasib (CodeBreaK 200), and total population of KRYSTAL-12 vs total population of CodeBreaK 200 (Table 3). Standardized mean differences (SMD) were used to describe imbalances in patient characteristics, with a SMD > 0.1 denoting a meaningful difference [25]. CodeBreaK 200 and KRYSTAL-12 had similar distribution of age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), disease stage, histology, liver and bone metastases. KRYSTAL-12 had a higher proportion of Asian population than CodeBreaK 200, although region was reported in KRYSTAL-12 rather than race. KRYSTAL-12 also showed a higher proportion of concurrent prior chemotherapy and immunotherapy. Compared to CodeBreaK 200, more patients in KRYSTAL-12 had PD-L1 expression from 1% to 50%, but fewer patients in KRYSTAL-12 had PD-L1 expression ≥50%.

Table 3. Patient characteristics of CodeBreaK 200 and KRYSTAL-12

Variable	Category	CodeBreaK 200			KRYSTAL-12				
		Sotorasib	Docetaxel	Total	Adagrasib	SMD^	Docetaxel	Total	SMD€
ITT population	N	171	174	345	301		152	453	
Safety population	N	169	151	320	298		140	438	
Age	Median	64	64	64	64		65	64.34	
	Range	32-88	35-87		34-83		45-80		
Sex	Female, %	36%	45%	41%	36%		28%	33%	
	Male, %	64%	55%	59%	64%	0.01	72%	67%	0.16
Race	Non-Asian‡, %	88%	87%	88%	74%		74%	74%	
	Asian, %	12%	13%	12%	26%	0.35	26%	26%	0.35
ECOG PS	0, %	35%	34%	34%	32%		31%	32%	
	1, %	65%	66%	66%	68%	0.05	68%	68%	0.05
Smoking	Never, %	3%	5%	4%	6%		6%	6%	
	Former, %	78%	75%	77%	76%	-0.06	74%	75%	-0.03
	Current, %	19%	20%	19%	19%	0.01	20%	19%	0.00
Disease stage	Locally advanced, %	5%	5%	5%	6%		5%	6%	
	Metastatic, %	95%	95%	95%	94%	-0.03	95%	94%	-0.03
Histology	Other, %	4%	6%	5%	6%	0.09	3%	5%	0.00
	Adenocarcinoma, %	96%	94%	95%	94%		97%	95%	
Prior chemo + IO	Sequential, %	53%	51%	52%	27%		27%	27%	
	Concurrent, %	47%	49%	48%	73%	0.54	73%	73%	0.52
	Did not receive both	Not included in the percentage calculation							
PD-L1 expression	<1%, %	35%	33%	34%	23%		26%	24%	
	≥1% to <50%, %	28%	42%	35%	49%	0.43	52%	50%	0.30
	≥50%, %	37%	24%	30%	28%	-0.19	22%	26%	-0.10
	Unknown	Not included in the percentage calculation							
Brain metastases£	No, %	77%	83%	80%	74%		76%	75%	
	Yes, %	23%	17%	20%	26%	0.06	24%	25%	0.12
Liver metastases†	No, %	86%	89%	88%	85%		88%	86%	
	Yes, %	14%	11%	12%	15%	0.03	12%	14%	0.04
Bone metastases†	No, %	73%	78%	76%	77%		74%	76%	
	Yes, %	27%	22%	24%	23%	-0.09	26%	24%	-0.01

^ The standardized mean difference (SMD) was calculated for adagrasib arm (KRYSTAL-12) vs sotorasib (CodeBreaK 200). A SMD ≥ 0.1 was highlighted in orange, indicating meaningful differences between two cohorts compared
€ This SMD was calculated for total population of KRYSTAL-12 vs total population of CodeBreaK 200
£ In both CodeBreaK 200 and KRYSTAL-12, baseline brain metastases identified post-hoc by using a CNS imaging charter and independent neuroradiologist review of brain imaging will be used in the current analysis. Refer to Section 8.6.6.3 for detailed explanations
† Metastases at baseline was based on blinded independent central review
‡ In CodeBreaK 200, Black or African American, White, multiple, other, unknown were grouped as non-Asian; in KRYSTAL-12, region (Asia-Pacific vs non-Asia-Pacific) was reported rather than race
Number of prior lines of therapy was not reported for KRYSTAL-12

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; IO, immunotherapy; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; SMD, standardized mean difference

CodeBreaK 200 and KRYSTAL-12 reported PFS and ORR as efficacy outcomes (Table 4). OS data was not reported at the data cut off date (31 December 2023) for KRYSTAL-

12. CodeBreaK 200 and KRYSTAL-12 reported the safety outcomes with a focus on treatment-related adverse events (TRAE) (Table 5).

Table 4. Efficacy outcomes reported in CodeBreaK 200 and KRYSTAL-12

	CodeBreaK 200		KRYSTAL-12	
	Sotorasib	**Docetaxel**	**Adagrasib**	**Docetaxel**
ITT population, N	171	174	301	152
Median follow-up month	17.7		7.2	
PFS definition	PFS by BICR (RECIST v1.1): Time from randomisation until disease progression or death from any cause, whichever occurred first		PFS by BICR (RECIST v1.1): Time from randomization until disease progression or death from any cause, whichever occurs first	
Median PFS month (95% CI)	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)	5.5 (4.5, 6.7)	3.8 (2.7, 4.7)
PFS HR (95% CI)	0.66 (0.51, 0.86)	Reference	0.58 (0.45, 0.76)	Reference
PFS KM curve available	Yes	Yes	Yes	Yes
OS definition	Time from randomization to death from any cause		Time from date of randomization to date of death due to any cause	
Median OS month (95% CI)	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)	NA	NA
OS HR (95% CI)	1.01 (0.77, 1.33)	Reference	NA	NA
OS KM curve available	Yes	Yes	No	No
ORR definition*	ORR by BICR (RECIST v1.1): percent of patients documented to have a confirmed CR or PR		ORR by BICR (RECIST v1.1): percent of patients documented to have a confirmed CR or PR	
ORR	28%	13%	32%	9%
ORR OR (95% CI)	2.60 (1.48, 4.56)	Reference	4.68 (2.56, 8.56)	Reference

* In KRYSTAL-12, ORR stands for objective response rate, and it has the same definition as overall response rate in CodeBreaK 200

Abbreviations: BICR, blinded independent central review; HR, hazard ratio; ITT, intention-to-treat; KM, Kaplan-Meier; NA, not available; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors

Table 5. Safety outcomes reported in CodeBreaK 200 and KRYSTAL-12

	CodeBreaK 200		KRYSTAL-12	
	Sotorasib	**Docetaxel**	**Adagrasib**	**Docetaxel**
Safety population, N	169	151	298	140
TRAEs	70%	86%	94%	86%
Grade ≥3 TRAEs	33%	40%	47%	46%
TRAEs leading to discontinuation	9%	11%	8%	14%
TRAEs leading to dose reduction	15%	26%	48%	24%
TRAEs leading to dose interruption	36%	15%	59%	19%
Treatment-related deaths	1%	1%	1%	1%
Individual TRAE (any grade)*				
Diarrhea, any grade TRAE	34%	19%	53%	30%
Nausea, any grade TRAE	14%	20%	34%	29%

	CodeBreaK 200		KRYSTAL-12	
Decreased appetite, any grade TRAE	11%	14%	23%	21%
ALT increased, any grade TRAE	10%	0%	30%	3%
AST increased, any grade TRAE	10%	0%	30%	0%
Fatigue, any grade TRAE	7%	25%	15%	14%
Vomiting, any grade TRAE	5%	7%	35%	7%
Asthenia, any grade TRAE	4%	11%	18%	28%
Individual TRAE (grade ≥ 3)*				
Diarrhea, grade ≥ 3 TRAE	12%	2%	5%	4%
Nausea, grade ≥ 3 TRAE	1%	1%	3%	10%
Decreased appetite, grade ≥ 3 TRAE	2%	0%	1%	1%
ALT increased, grade ≥ 3 TRAE	8%	0%	8%	0%
AST increased, grade ≥ 3 TRAE	5%	0%	6%	0%
Fatigue, grade ≥ 3 TRAE	1%	6%	3%	2%
Vomiting, grade ≥ 3 TRAE	0%	0%	2%	1%
Asthenia, grade ≥ 3 TRAE	1%	3%	4%	10%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse events

* Individual TRAEs were selected, if they were among both, the top 10 AEs for sotorasib (CodeBreaK 200) and adagrasib (KRYSTAL-12)

Overall, CodeBreaK 200 and KRYSTAL-12 share a similar study design and demonstrate a good balance on most baseline characteristics. Due to early dropout, crossover and protocol deviations in both CodeBreaK 200 [8] and KRYSTAL-12, the comparator arm of the two trials were prone to significant bias . The magnitude of bias in the comparator arm of CodeBreaK 200 and KRYSTAL-12 appears to be different. The early dropout rate in the docetaxel arm of CodeBreaK 200 was 65% higher compared to the early dropout rate in the docetaxel arm in KRYSTAL-12. Furthermore, due to changes in the study design while the trial was already ongoing, there was significant informative censoring and crossover outside of the protocol in CodeBreaK 200. Informative censoring occurred, when patients progressed due to investigator assessment and subsequent confirmation-of-progression while not yet having progressed as per BICR. This is expected to overestimate PFS of docetaxel in CodeBreaK 200. Out-of-protocol crossover resulted in subjects taking sotorasib while being in the comparator arm which potentially affected PFS assessment. Significant bias in the docetaxel arm was acknowledged by regulatory bodies and resulted in not accepting CodeBreaK 200 as a confirmatory trial. Furthermore, despite being present in the comparator arm, this bias did not occur in the sotorasib or adagrasib arm from CodeBreak 200 and KRYSTAL-12 trials, respectively. Given these limitations, an unanchored MAIC that compares sotorasib arm and adagrasib arm will be conducted as

the primary analysis. An anchored MAIC that uses docetaxel arm as the anchor will be conducted as a sensitivity analysis.

8.2 Effect Measures

The analyses will use HRs as relative effect estimate for the time-to-event PFS, and ORs for ORR and AEs.

8.3 Obtain Estimates from Individual Studies

Patient-level data is not available for the KRYSTAL-12 trial. Therefore, KM curves will be digitized using the Engauge Digitizer to convert the image files of the KM survival curves from the study publications into numeric values (i.e., time and corresponding survival probabilities) [26]. These coordinates will then be used to generate pseudo IPD (i.e., time and censoring status) for each curve in R using a validated algorithm by Guyot 2012 [9]. To assess the quality of the data digitization, the reconstructed KM data from the pseudo patient-level data will be compared to the published results from the KRYSTAL-12 trial, such as median PFS. Dichotomous outcome data (i.e., ORR and AE) will be extracted as the number of patients with events along with the total numbers of patients assessed.

These pseudo IPD and the dichotomous data for KRYSTAL-12, as well as IPD of CodeBreaK 200, will be used to generate effect estimates within each study, followed by indirect comparison, using the methods described in Section 8.6.

8.4 Heterogeneity

Covariates identified by discussion with clinical experts and literature to be prognostic variables and/or effect modifiers for prognosis in NSCLC will be used to adjust for the observed heterogeneity across studies (see Section 8.6.5).

8.5 Missing Data

Available data on the baseline characteristics and information on outcome data are presented in Section 8.1.

In MAIC analysis, a patient will be excluded from analysis if information on one or more matching covariates required in the model was missing, or if a patient had missing information on the outcome analyzed. No imputation will be performed for missing values.

8.6 Statistical Analysis

8.6.1 Primary Analysis Set

The CodeBreaK 200 and KRYSTAL-12 studies will form the primary analysis set. For efficacy analysis, the ITT population for CodeBreaK 200 and KRYSTAL-12 will be used. For the analysis of AEs, the population evaluated for safety in each trial will be used.

8.6.2 Primary Outcome

The primary outcomes used to assess the comparative efficacy of sotorasib vs adagrasib are PFS and ORR. OS for KRYSTAL-12 was not yet reported, therefore it was not possible to be included as an outcome.

The primary outcomes used to assess the safety of sotorasib vs adagrasib are any TRAEs, Grade ≥3 TRAEs, TRAEs leading to discontinuation, TRAEs leading to dose reduction, TRAEs leading to dose interruption, and individual TRAEs of any grade (i.e. diarrhea, nausea, decreased appetite, ALT increased, AST increased, fatigue, vomiting, asthenia). Individual TRAEs were selected, if they were among both, the top 10 AEs for sotorasib (CodeBreaK 200) and adagrasib (KRYSTAL-12). The AEs, blood alkaline phosphate increase and abdominal pain, were among the top 10 AEs for sotorasib (CodeBreaK 200) but not reported for adagrasib (KRYSTAL-12). Therefore, it will not be possible to include these for analysis. Correspondingly, the AEs, blood creatinine increased and anemia, were among the top 10 AEs for adagrasib (KRYSTAL-12) but not among the top 10 AEs for sotorasib (CodeBreaK 200). Inclusion of these AEs would have been an asymmetric approach putting sotorasib into advantage. Therefore, these AEs will also be excluded. Analysis of grade ≥3 individual TRAEs will not be conducted due the low event rates for most of the individual TRAEs in both CodeBreaK 200 and KRYSTAL-12 that could lead to unstable estimates (Table 5).

A description of how the outcomes will be analyzed is summarized in the MAIC section (Section 8.6.6).

8.6.3 Secondary Outcomes

Not applicable.

8.6.4 Confounding

A list of covariates (Table 6) was identified to have a prognostic impact for NSCLC based on extensive documented discussions with NSCLC physicians [27] and from review of other MAIC studies in NSCLC (this list is broader than the covariates selected for adjustment in the current study). Interviews with six different medical oncologists with

extensive experience of treating patients with advanced NSCLC were conducted via teleconferences. Of the six interviewed physicians, two were practicing in Canada, one in the United States, one in Germany, one in France and one in the United Kingdom. All six physicians unanimously agreed that ECOG PS was the most important factor to predict prognosis of advanced NSCLC patients. Other factors that were indicated to be very important by a majority of physicians (at least 4) were the presence of brain metastases, disease stage, PD-L1 protein expression, and presence of other gene alterations. Table 6 also lists several other factors considered as being somewhat important for prognosis by majority of physicians (at least 4), as well as additional baseline covariates reported in other MAICs.

Table 6. Covariates identified by NSCLC physicians to have a prognostic impact (this list is broader than the covariates selected for adjustment)

Category	Covariate
Very important	Baseline ECOG PS
	Brain metastases at baseline (Y; N)
	Disease stage (locally advanced, metastatic)
	PD-L1 protein expression (<1%, 1–49%, ≥ 50%) (relevant only for patients who are receiving an anti-PD(L)1 in line of therapy of interest)
	Presence of other gene alterations (e.g., ALK, EGFR, ROS1, STK11/LKB1, KEAP1, BRAF, TP53, etc.)
Somewhat important	Age (18-64 years, 65–74 years, 75+ years)
	BMI at baseline
	Smoking history (never smoked, current, former, missing)
	Liver metastases at baseline (Y; N)
	Bone metastases at baseline (Y; N)
	Number of sites of metastases at baseline (0 vs 1 vs 2 vs 3 or more)
	Number of prior lines of therapy (1, 2 or 3 or more)
	Types of therapies administered in prior lines (platinum-based chemotherapy + PD-1 or PD-L1)
	Time from prior line initiation to the index date (months)
	Albumin at baseline
	Serum LDH at baseline
	Liver function (ALT, AST) at baseline
	Renal function (eGFR) at baseline
	Sex (F; M)
	Race/Ethnicity (Asian; Black or African American; White; Other)

Additional covariates reported in other MAIC	Histology at baseline (Non-squamous; squamous)

Abbreviations: ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase, AST; aspartate aminotransferase; BMI, body mass index; BRAF, B-Raf proto-oncogene, serine/threonine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth receptor factor; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; MAIC, matching-adjusted indirect comparison; PD-L1, programmed death ligand-1; ROS-1, c-ros oncogene 1

To provide further context, covariates used for matching in previously published MAICs in NSCLC were reviewed. An MAIC analysis in patients with PD-L1 TPS ≥1% metastatic NSCLC included age, sex, geographic region, ECOG PS, smoking status, histology, sites of metastases and PD-L1 expression [18]. In a comparison of treatments in *ALK*+ patients with NSCLC, Reckamp et al. considered the covariates of Asian ethnicity, ECOG PS, smoking status, prior therapy and response, number of metastatic sties and brain metastases [19]. An analysis in patients with *ROS1*+ NSCLC selected sex, ECOG PS, smoking history, age, prior treatment and disease stage at enrollment as covariates [16].

Levels of categorical variables may be combined, especially when there are few events (i.e., <5) within a level of a categorical baseline variable.

8.6.5 Covariates

Depending on the level of importance presented in Table 6, availability and balance of covariates as observed in both trials, the base case model (Model 1) will include age, sex, race, prior chemotherapy + immunotherapy (chemo + IO), brain metastases, and liver metastases (Table 7); the sensitivity analysis model (Model 2) will include ECOG PS, disease stage, bone metastases, PD-L1 expression, and smoking history in addition to all variables included in the base case model.

The base case model would be parsimonious and would leverage more sample size and better confidence in the results compared to the inclusive sensitivity analysis model.

Despite ECOG PS being determined as an important prognostic indicator in advanced NSCLC, the threshold for poor outcomes is usually a PS score of 2 and above. In contrast, CodeBreaK 200 and KRYSTAL-12 only included patients with an ECOG PS of 0 or 1. Furthermore, the ECOG PS distribution between the overall population of both trials appeared comparable. Therefore, ECOG PS will not be included in the base case model and will be adjusted for in the sensitivity model.

Prior chemo + IO (sequential vs concurrent chemo / IO usage) will be included in the base case model as it has been found that using IO in the line prior to sotorasib can lead

to increased AEs (e.g., hepatotoxicity). Additionally, since number of prior lines of therapy is an important prognostic variable but is not reported for KRYSTAL-12, adjusting for prior chemo + IO should potentially account for some of the confounding which might be attributed to not adjusting for number of prior lines of therapy.

PD-L1 protein expression, according to the physician insights report, is only a strong predictor if IO treatment is involved. For the current study, neither sotorasib, adagrasib nor docetaxel are IO treatments. Furthermore, prior chemo and IO usage (unless non-eligible) is adjusted in the base-case model which should potentially account for confounding which might be associated with PD-L1 expression. Therefore, the variable will not be included in the base case analysis. A further rationale against inclusion is a non-trivial proportion of subjects with missing PD-L1 expression in KRYSTAL-12 (14% for adagrasib). In contrast, for CodeBreaK 200 the PD-L1 protein expression was missing only for 8 sotorasib patients (4.7%). PD-L1 expression will be included in the sensitivity model.

The gene alterations are neither included for adjustment in the base case analysis nor in the sensitivity model as this information is not reported for KRYSTAL-12, and including a series of co-mutations would have yielded a massive drop in ESS.

Race (Asian vs. Non-Asian) is included as a covariate in the base case model. It is not only known as an important predictor in the literature [28]; its prognostic effect was also observable in CodeBreaK 100 and CodeBreaK 200. In KRYSTAL-12, region (Asia-Pacific vs non-Asia-Pacific) was reported in KRYSTAL-12 instead of race. Therefore, if region can be derived from the IPD of CodeBreaK 200, it will be used to match the definition in KRYSTAL-12.

Table 7. Covariates to be included in base case model (Model 1) or sensitivity analysis model (Model 2)

Covariate	Category	Model 1	Model 2
Age	Continuous	✓	✓
Sex	Female vs Male	✓	✓
Race*	Asian vs Non-Asian	✓	✓
Prior chemo + IO	"Concurrent chemo + IO" vs "Sequential chemo + IO"	✓	✓
Brain metastases^	Yes vs No	✓	✓
Liver metastases	Yes vs No	✓	✓
ECOG PS	0 vs 1		✓
Bone metastases	Yes vs No		✓
Disease stage	Metastatic vs Locally advanced		✓

PD-L1	<1% vs 1–49% vs ≥ 50%	✓
Smoking history	Current vs Former vs Never	✓

* Race was reported in CodeBreaK 200, region (Asia-Pacific vs non-Asia-Pacific) was reported in KRYSTAL-12. Region may be used for CodeBreaK 200 to match the definition in KRYSTAL-12 if it can be derived from the individual patient level data of CodeBreaK 200

^ In both CodeBreaK 200 and KRYSTAL-12, baseline brain metastases identified by using a CNS imaging charter and independent neuroradiologist review of brain imaging will be used in the current analysis. Refer to Section 8.6.6.3 for detailed explanations

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IO, immunotherapy; PD-L1, programmed death ligand-1

8.6.6 Match Adjusted Indirect Comparisons (MAIC)

The premise of the MAIC is to adjust for between-trial differences in baseline characteristics acting as prognostic factors/effect modifiers. MAIC is a non-parametric likelihood reweighting method that allows a propensity score logistic regression model to be estimated without individual patient data in one of the treatment arms [29].MAIC approach will be used for the indirect comparison between sotorasib (CodeBreaK 200) and adagrasib (KRYSTAL-12).

As discussed in Section 8.1, both unanchored and anchored comparisons are feasible. However, Due to early dropout, crossover and protocol deviations in both CodeBreaK 200 [8] and KRYSTAL-12, the comparator arm of the two trials were prone to significant bias. The magnitude of bias in the comparator arm of CodeBreaK 200 and KRYSTAL-12 appears to be different. The early dropout rate in the docetaxel arm of CodeBreaK 200 was 65% higher compared to the early dropout rate in the docetaxel arm in KRYSTAL-12. Furthermore, due to changes in the study design while the trial was already ongoing, there was significant informative censoring and crossover outside of the protocol in CodeBreaK 200. Informative censoring occurred, when patients progressed due to investigator assessment and subsequent confirmation-of-progression while not yet having progressed as per BICR. This is expected to overestimate PFS of docetaxel in CodeBreaK 200. Out-of-protocol crossover resulted in subjects taking sotorasib while being in the comparator arm which potentially affected PFS assessment. Significant bias in the docetaxel arm was acknowledged by regulatory bodies and resulted in not accepting CodeBreaK 200 as a confirmatory trial. Furthermore, despite being present in the comparator arm, this bias did not occur in the sotorasib or adagrasib arm from CodeBreak 200 and KRYSTAL-12 trials, respectively.

Given these limitations, an unanchored MAIC that compares sotorasib arm and adagrasib arm will be conducted as the primary analysis. An anchored MAIC that uses docetaxel arm as the anchor will be conducted as a sensitivity analysis. The prognostic

variables and effect modifiers selected for MIAC adjustment have been detailed in Section 8.6.4 and Section 8.6.5.

In the following description of MAIC methodology, CodeBreaK 200 is referred to as the index trial with sotorasib as the index treatment, and KRYSTAL-12 is referred to as the comparator trial with adagrasib as the comparator treatment.

8.6.6.1 Estimation of Weights

The first step in conducting the MAIC involves deriving balancing weights such that the average baseline characteristics of the index trial (CodeBreaK 200) will match the published aggregate characteristics of the comparator trial (KRYSTAL-12) after re-weighting. A propensity score-type logistic regression equation will be used to estimate the weights; this equation will predict whether a given type of patient originated from the index trial or the comparator trial as a function of baseline characteristics. Specifically, weights will be estimated by the odds calculated as $w_i = exp(\alpha + x_i'\beta)$, where x_i' is the vector of baseline variables included for matching and α is the intercept. The β coefficients will be determined by the method of moments rather than the maximum likelihood (as is usually the case), because only aggregate data for the x's is available for the competitor populations [14, 30].

Once the coefficients are estimated, the equation will be applied to the patients from the index trial to calculate the individual patient weights. These weights will then be used to calculate the effective sample size (ESS) achieved as $(\sum w_i)^2/(\sum w_i^2)$ where w_i is the calculated weight for each individual patient (i). If the populations are perfectly balanced before adjustment, all patients would have $w_i = 1$, and the ESS would be equal to the original size of patients in the index trial. Adjustments for population differences will assign patients uneven weights, leading to the inevitable loss of ESS.

A small ESS usually indicates little overlap between baseline characteristics of the two trials and an irregular distribution of weights across patients, which can lead to unstable or invalid estimates [10]. In the situation where the resulting ESS from MAIC is too small (e.g., less than 40% of the original sample size), or the regression model for indirect comparison does not converge, the analysis will be deemed infeasible. Certain variable categories can be combined or characteristics not differing between the two trials before matching can be omitted in case of convergence issues.

In the weight calculation, patients with missing values for any of the adjusted prognostic variables or effect modifiers will be excluded to ensure that information is available for all

variables used in the adjustment. After calculating the individual patient's weights, the distribution of weights will be assessed using rescaled weights by dividing each w_i by their sum $(\sum w_i)$ and then multiplying by sample size, and overly influential observations will be identified (e.g., weights greater than +/- 3 times the standard deviation from the average weight [31]). Trimming extreme weights will be considered when necessary.

8.6.6.2 Primary analysis

In the primary analysis, an unanchored MAIC will be conducted, adjusting for age, sex, race, prior chemo + IO, brain metastases, and liver metastases (Section 8.6.5).

To perform an indirect comparison for PFS, the time-to-event data from the index trial with MAIC weights and the digitized pseudo IPD from the comparator trial will be used. Weighted Cox regression with a robust variance estimator will be used to generate hazard ratios and their 95% confidence intervals (CIs) that reflect the expected relative effect between the index and the comparator treatments for PFS in a population of the index trial matching the characteristics of the comparator trial. Naïve comparison will also be conducted using Cox regression without any re-weighting or variable adjustment.

To perform an indirect comparison for ORR and AEs, the outcome of each individual patient from the index trial with MAIC weights, and the number of patients with events as assessed in the comparator trial will be used. Weighted logistic regression with a robust variance estimator will be used to generate odds ratios and their 95% confidence intervals (CIs) that reflect the expected relative effect between the index and the comparator treatments on ORR or AEs. Naïve comparison will also be conducted using logistic regression without any re-weighting or variable adjustment.

8.6.6.3 Subgroup Analysis

In terms of subgroup analyses, efficacy outcomes will be evaluated for patients with treated/stable brain metastases. Approximately 40% of patients with *KRAS* G12C-mutant NSCLC develop brain metastases and there is a high unmet need for effective therapies in this population [32].

The KRYSTAL-12 and CodeBreaK 200 studies conducted post-hoc analyses of clinical outcomes in patients with baseline brain metastases. In both post-hoc analyses, patients with baseline brain metastases were identified using a CNS imaging charter and independent neuroradiologist review of brain imaging [6, 7, 13, 33]. Systemic PFS per BICR (according to standard RECIST v1.1 criteria) were reported in this patient subgroup. Additionally, intracranial PFS was assessed according to CNS-adapted

RECIST v1.1 criteria (in KRYSTAL-12) and RANO-BM criteria (in CodeBreaK 200). Given the differences between CNS-adapted RECIST v1.1 versus RANO-BM for measuring intracranial PFS, the current analysis will focus on systemic efficacy (PFS) in patients with baseline brain metastases identified by independent neuroradiologist review.

For comparison of efficacy outcomes (PFS using KM curves), the matching weights will be re-calculated, based on the covariate distribution in the corresponding subgroups of patients with brain metastases. Variables in the base case model (Table 7), including age, sex, prior chemo + IO, and liver metastases, will be adjusted in the subgroup analysis; race or region was not reported for the patient subgroup with brain metastases in KRYSTAL-12, and therefore, cannot be adjusted.

Given the above limitations with the covariate distributions and definition of brain metastases, conducting a comparison in the subgroup of subjects with brain metastases is challenging. Yet, given the clinical discussion around efficacy differences in this subgroup, it is important to spot whether there are any signs of differences in efficacy. Acknowledging the challenges, prior to conducting any adjusted analyses, a naive comparison will be performed. In addition, to get a more balanced understanding, an adjusted analyses will be conducted.

8.6.6.4 Sensitivity analysis

A summary of the planned sensitivity analyses to compare sotorasib vs adagrasib are presented in Table 8. In Sensitivity Analysis 1, ECOG PS, disease stage, bone metastases, smoking history, and PD-L1 expression will also be included in the adjustment, in addition to the variables adjusted in base case. In Sensitivity Analysis 2, anchored comparison will be conducted, adjusting for the same variables as in the base case.

Table 8. Base case, sensitivity, and subgroup analysis

Analysis	MAIC type	Population	Outcome	Variable adjusted
Base case	Unanchored	ITT populations for efficacy, safety populations for AEs	PFS, ORR, AE outcomes where event rate allows analysis	Age, sex, race/region, prior chemo + IO, brain metastases*, liver metastases
Sensitivity analysis 1	Unanchored	ITT populations for efficacy, safety populations for AEs	PFS, ORR, AE outcomes where event rate allows analysis	Age, sex, race/region, prior chemo + IO, brain metastases*, liver metastases, ECOG PS, disease stage, bone metastases, smoking history, PD-L1

Sensitivity analysis 2	Anchored	ITT populations for efficacy, safety populations for AEs	PFS, ORR, AE outcomes where event rate allows analysis	Age, sex, race/region, prior chemo + IO, brain metastases*, liver metastases

* In both CodeBreaK 200 and KRYSTAL-12, baseline brain metastases identified by using a CNS imaging charter and independent neuroradiologist review of brain imaging will be used in the current analysis. Refer to Section 8.6.6.3 for detailed explanations

Abbreviations: AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; IO, MAIC, match adjusted indirect comparisons; immunotherapy; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression free survival

In sensitivity analysis 2 using anchored MAIC, with the weights generated by MAIC, weighted Cox regression or weighted logistic regression will be conducted using the index trial data to estimate the adjusted hazard ratio or adjusted odds ratio between the two treatments in the index trial (i.e., sotorasib vs. docetaxel). For binary outcome analysis using logistic regression, if at least one of the categories has zero patient, the analysis would be deemed infeasible because the odds would not be able to be estimated. For example, in CodeBreaK 200, the docetaxel arm had 0% patients who experienced ALT increased (any grade) and AST increased (any grade) (Table 5), therefore, anchored comparison for these two individual TRAEs will not be feasible.

The relative effect measure between the index treatment and the comparator will be calculated by subtracting the adjusted hazard ratio or adjusted odds ratio of the index trial and the hazard ratio or odds ratio of the comparator trial at log scale [35]. Naïve comparison will also be conducted using the unadjusted hazard ratios or odds ratios. Using the estimated variance of the hazard ratios or odds ratios, Wald-type normal distribution-based CIs will be constructed for the relative effect estimates.

8.6.6.5 Reporting of results

Summary statistics of baseline patient characteristics will be reported for the index trial prior to and after MAIC matching, as well as for the comparator trial. Percentage will be reported for categorical variables, and mean will be reported for continuous variables. The ESS and the percentage of ESS compared to the original sample size will also be reported for the index trial. For continuous variables, in cases where only median values were available from the comparator trial, the mean will be assumed equal to the median.

Estimates of the relative treatment effect comparing the index and the comparator treatments will be presented in data tables, including ESS, hazard ratios or odds ratios with 95% CIs, p values of log-rank test (Cox regression) or p values of Wald test (logistic regression). For unanchored comparisons, the naïve and MAIC-weighted Kaplan-Meier curves of the index treatment, and the reproduced Kaplan-Meier curve of the comparator will be plotted.

All regressions will use the comparator as the reference group. In the analyses of PFS, a hazard ratio greater than one would indicate a lower survival probability of the index treatment compared with the reference (i.e., in favor of the reference), while a hazard ratio of less than one would indicate a higher survival probability of the index treatment (i.e., in favor of the index treatment). In the analyses of ORR, an odds ratio greater than one would indicate a higher odds of achieving ORR compared with the reference (i.e., in favor of the index treatment), while an odds ratio less than one would indicate a lower odds of achieving ORR for the index treatment (i.e., in favor of the reference). In the analyses of AEs, an odds ratio greater than one would indicate a higher odds of having the event compared with the reference (i.e., in favor of the reference), while an odds ratio less than one would indicate a lower odds of having the event for the index treatment (i.e., in favor of the index treatment). A 95% CI that does not include one or a p value less than 0.05 would indicate statistical significance.

8.6.7 Sensitivity Analysis

See Section 8.6.6.3.

8.6.8 Subgroup Analysis

See Section 8.6.6.3.

9. STUDY LIMITATIONS

As with any indirect treatment comparison, differences in the methodology, outcome measurement and populations of the included trials must be carefully considered. MAICs are not randomized comparisons and cannot be interpreted as such.

Unanchored MAIC assumes that all effect modifiers and prognostic factors are accounted for, with failure of this assumption leading to an unknown amount of residual bias. Given the minimal differences in patient populations in the current MAIC analysis, the bias is expected to be low. The analysis will be able to adjust for the major confounding factors highlighted by discussions with NSCLC physicians and those used in literature, including age, sex, race, prior chemo + IO, brain metastases, and liver metastases in the base case model, with the addition of ECOG PS, disease stage, bone metastases, smoking history, and PD-L1 in the sensitivity model. Certain important variables, such as presence of other gene alterations and number of prior lines of therapy, were not available in KRYSTAL-12 and therefore cannot be adjusted. However, adjusting for prior chemo + IO and PD-L1 should potentially account for most of the confounding which might be attributed to number of prior lines of therapy as an unmeasured confounder. For the subgroup analysis of patients with brain metastases,

race or region information is not available for this subgroup in KRYSTAL-12, and therefore, cannot be adjusted in MAIC. Additionally, considering the relatively small sample sizes of this subgroup in both trials, only the base case covariate adjustment (without race) will be conducted to ensure an analyzable ESS.

Certain variables may be reported differently between the two trials. For example, race (Asian vs non-Asian) was reported in CodeBreaK 200 whereas region (Asia-Pacific vs non-Asia-Pacific) was reported in KRYSTAL-12. If region can be derived from IPD, it may be used for CodeBreaK 200 to match the definition in KRYSTAL-12.

For subgroup of patients brain metastases, post-hoc evaluation of brain metastases identified by using a CNS imaging charter and independent neuroradiologist review of brain imaging was conducted in both trials. The CB200 trials used modified RANO-BM criteria and the KRYSTAL-12 trials assessed using CNS-adapted RECIST v1.1;

Additionally, the MAIC approach can only account for differences in patient-level characteristics that affect outcomes, while other differences at the study-level remain unaccounted for.

For survival outcomes where IPD is not available for KRYSTAL-12, the pseudo-IPD of the KRYSTAL-12 will be obtained via digitization. Although digitization of Kaplan-Meier survival curves using statistical methods (e.g., Guyot) can “recreate” numerical values and provide a reasonable estimate, it may not perfectly replicate true patient-level data.

Lastly, the generalizability of this analysis will be limited to the patients included in the CodeBreaK 200 and KRYSTAL-12 trials, and may not reflect the real-world practice and population.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Adverse Events

Reporting of individual adverse events (AE), product complaints (PCs), and other safety findings are not applicable for SLRs, which involve published literature sources, as the safety data from the studies identified will have been previously reported to regulatory agencies, institutional review boards, and ethics committees in accordance with local regulations and routine pharmacovigilance practices.

10.2 Subject Confidentiality

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or collection of additional subject data will occur. Study results will be in tabular form and aggregate analyses that omit subject identification. Any publications and reports will not include subject identifiers.

11. ADMINISTRATIVE AND LEGAL OBLIGATIONS

11.1 Study Amendments and Study Termination

Amendments must be made only with the prior approval of Amgen.

11.2 Study Documentation and Archive

Retention of study documents will be governed by the contractual agreement with the vendor and will be maintained pursuant to Amgen's records retention schedule.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results from the study would be used for communication with external stakeholders enabling a strong case for sotorasib.

12.1 Publication Plan

As this study informs the risk benefit of sotorasib, the study results need to be published as a publication or abstract as per SOP-429662 (v5.0) in line with the publication commitment.

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