Background Information

for

the Oncologic Drugs Advisory Committee

05 October 2023

Supplemental New Drug Application for Sotorasib

Submitted: 05 September 2023

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviation or Term	Definition/Explanation
ADRs	adverse drug reactions
ALT	alanine aminotransferase
ASCO	American Society for Clinical Oncology
AST	aspartate aminotransferase
BICR	blinded independent central review
CDF	cumulative distribution function
C_{max}	maximum plasma concentration
CNS	central nervous system
COVID-19	coronavirus-2019
CRC	colorectal cancer
CTCAE	common terminology criteria for adverse events
DCR	disease control rate
DMC	Data Monitoring Committee
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 13
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOI	event of interest
EQ-5D-5L	EuroQol-5 Dimension 5 Level
FACT-G	Functional Assessment of Cancer Therapy Tool - General form
FDA	Food and Drug Administration
HR	harard ratio
ILD	interstitial lung disease
ITT	intent-to-treat
IPCW	inverse probability of censoring weighting
IV	Intravenous(ly)
KRAS	Kirsten rat sarcoma viral oncogene homolog (protein)
KRAS	Kirsten rat sarcoma viral oncogene homolog (DNA)
$KRAS^{G12C}$	KRAS protein with a G12C amino acid substitution
KRAS p.G12C	KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level

Abbreviation or Term	Definition/Explanation
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PFS2	second progression-free survival analysis
PK	pharmacokinetic(s)
PRO	patient-reported outcomes
Q3W	once every 3 weeks
QD	once daily
QoL	quality of life
RANO-BM	Response Assessment in Neuro-Oncology Brain Metastases
RAS	rat sarcoma viral oncogene homolog
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	restricted mean survival time
SAP	statistical analysis plan
SEER	Surveillance, Epidemiology, and End Results
sNDA	supplemental New Drug Application
SMQ	standardized MedDRA Query
TTR	time to response
ULN	upper limit of normal
US	United States
VAS	visual analogscale
VEGF	vascular endothelial growth factor
WHO	World Health Organization

1. Executive Summary

Introduction

Sotorasib is a novel, first-in-class, potent, orally administered small molecule that selectively inhibits Kirsten rat sarcoma viral oncogene homolog protein (KRAS) with the G12C mutation ($KRAS^{G12C}$). Sotorasib was granted accelerated approval in the United States (US) on 28 May 2021 for the treatment of adult patients with Kirsten rat sarcoma viral oncogene homolog gene (*KRAS) p.G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an Food and Drug Administraton (FDA)-approved test, who have received at least 1 prior systemic therapy. As of 01 August 2023, sotorasib has been approved in more than 52 countries.

The original accelerated approval for sotorasib was supported by the phase 1 and phase 2 part A results from CodeBreaK 100 (Study 20170543), a multicenter, open-label, multicohort, single-group study. For patients with advanced NSCLC with the *KRAS* gene with a mutation resulting in a G12C amino acid substitution (*KRAS p.G12C*) mutation who received sotorasib at 960 mg daily in the phase 2 portion of CodeBreaK 100 (response evaluable population, n = 124), the objective response rate (ORR) as assessed by a blinded independent central review committee (BICR) was 36.3% (95% CI: 27.8, 45.4) and median duration of response (DOR) was 10 months (range 1.3+, 11.1). Most patients (n = 100) had received both prior platinum-based chemotherapy and immunotherapy. CodeBreaK 200 (Study 20190009), an ongoing phase 3 multicenter, randomized, open-label, active-controlled study of sotorasib compared with docetaxel for the treatment of previously treated locally advanced and unresectable or metastatic *KRAS p.G12C*-mutated NSCLC, was designed to provide confirmatory clinical data.

Amgen is seeking conversion from accelerated to traditional approval of sotorasib in the target indication, based on results from CodeBreaK 200.

Lung Cancer is the Leading Cause of Cancer Death

Worldwide, lung cancer (small cell and non-small cell) is the second most common cancer overall, with an estimated 2.21 million cases in 2020 (World Health Organization [WHO] Statistics, 2020). Most (80% to 90%) patients with a new diagnosis of lung cancer are current or former smokers (Siegel et al, 2021). Lung cancer causes more deaths than colon, breast, and prostate cancers combined. More than 80% of all lung cancer cases are classified as NSCLC and most patients with lung cancer (78%) are diagnosed with locally advanced or metastatic disease (stage IIIB or IV). Advanced NSCLC is a serious and life-threatening disease, with a 5-year survival rate of 9.3% (Surveillance, Epidemiology, and End Results [SEER], 2022). Advanced NSCLC is also associated with substantial symptom burden and comorbidities, which negatively affect patients' health-related quality of life (QoL). The *KRAS p.G12C* mutation is estimated to be present in 12% to 14% of NSCLC adenocarcinomoas in Western regions and is associated with smoking (Lee et al, 2022; Riely et al, 2008).

Unmet Medical Need for Effective and Tolerable Therapies for Patients With Advanced NSCLC Following Progression on First-line Treatment; a Serious and Life Threatening Disease

In clinical practice, patients with advanced NSCLC without actionable mutations are usually treated in first-line with a checkpoint inhibitor with or without chemotherapy. Approximately two-thirds of these patients progress in the first year (Jassem et al, 2021; Hellmann et al, 2019; Gandhi et al, 2018) and need second-line treatment options; however few recommended options exist for second-line treatment. In 1999, docetaxel

was approved for use after failure of prior platinum-based chemotherapy based on a demonstrated improvement in survival over best supportive care (Taxotere® prescribing information, 2020). The combination of docetaxel plus ramucirumab, a vascular endotheial growth factor (VEGF) inhibitor, has demonstrated a marginal improvement in survival as compared to docetaxel (hazard ratio [HR] = 0.86, 95% CI: 0.75, 0.98) (Garon et al, 2014) and is used less frequently than docetaxel alone in the US. However, this combination is associated with significant toxicity (serious adverse reactions include febrile neutropenia, pneumonia, and neutropenia; common adverse reactions include neutropenia fatigue/asthenia, and stomatitis/mucosal inflammation (Cyramza® prescribing information, 2020), and has limited usage globally. The option to use a checkpoint inhibitor in this setting is limited due to the majority of patients being treated with this therapy in the frontline setting.

Patients with advanced NSCLC (including those with tumors containing the *KRAS p.G12C* mutation) have poor treatment outcomes with existing therapies in second-line or later, and their prognosis is poor (Spira et al, 2021). In an observational study based on US-based electronic health record-derived de-identified databases, patients with *KRAS p.G12C*-mutated NSCLC had a median real-world overall survival (OS) and median real-world progression-free survival (PFS) in second-line or later docetaxel therapy of 6.0 (95% CI: 4.9, 7.1) months and 3.4 (95% CI: 2.7-4.2) months, respectively (Gray et al, 2023).

There is an important need for new treatments for patients with *KRAS p.G12C*-mutated NSCLC who have progressed after first-line treatment. Sotorasib can provide targeted therapeutic benefit to these patients without the challenges associated with the current standard of care, docetaxel (ie, modest response rates, serious toxicities, intravenous [IV] route of administration, poor tolerability) in advanced NSCLC.

KRAS p.G12C is a Common Mutation in NSCLC and Sotorasib Has Been Used Worldwide to Target This Mutant Protein Since 2021

Targeting mutant KRAS protein was a goal of cancer biologists for several decades. In 2013, the groundbreaking discovery of a cryptic pocket in KRAS enabled relatively specific small molecule inhibitors to be developed (Ostrem et al, 2013). Sotorasib is a small molecule inhibitor that covalently and selectively binds to the KRAS protein with a G12C amino acid substitution ($KRAS^{G12C}$) mutant protein and locks it in an inactive state. This blocks the interaction of $KRAS^{G12C}$ with effectors, thereby preventing downstream MAPK pathway signaling and tumorigenesis.

A Robust Clinical Program Demonstrates the Efficacy of Sotorasib in Treating Advanced NSCLC With the *KRAS p.G12C* Mutation

Efficacy of sotorasib has been assessed in approximately 600 patients with locally advanced or metastatic NSCLC (171 patients in CodeBreaK 200 and 469 patients in CodeBreaK 100 including more than 200 patients in phase 2 part B):

- CodeBreaK 200, which is the phase 3 confirmatory study comparing the safety and efficacy of sotorasib (171 patients) with the active comparator docetaxel (174 patients), demonstrated that treatment with sotorasib results in rapid, durable tumor responses, higher overall response rates, and improved progression-free survival (PFS) in patients receiving orally administered sotorasib over IV-administered docetaxel in a post-platinum chemotherapy/immunotherapy-treated study population, thereby confirming the clinical benefit of sotorasib.
- CodeBreaK 100 phase 2 part A, which was the study supporting accelerated approval (124 patients with *KRAS p.G12C*-mutated locally advanced or metastatic

NSCLC) showed consistent efficacy and safety results with CodeBreaK 200 and CodeBreaK 100 phase 1 part B.

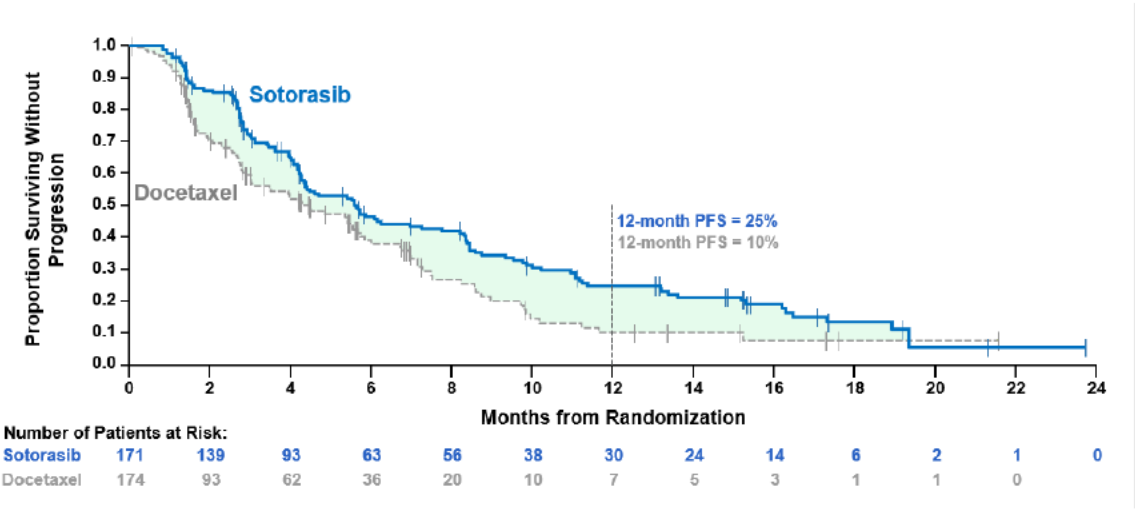
- The dose comparison study (part of CodeBreak 100), a randomized phase 2 study comparing the safety and efficacy of 960 mg sotorasib (104 patients) vs 240 mg sotorasib (105 patients), provides supporting data showing that treatment with sotorasib demonstrates consistent and clinically meaningful responses in patients with *KRAS p.G12C*-mutated NSCLC.

CodeBreaK 200 Key Efficacy Results:

Progression-free Survival: Primary Endpoint

- The study met its primary endpoint: sotorasib lowered the risk of disease progression or death compared with docetaxel: the hazard ratio [HR] for PFS was 0.663 (95% CI: 0.509, 0.864; $p = 0.003$), demonstrating a 34% reduction in the risk of progression or death compared with docetaxel.
- Kaplan-Meier PFS curves showed early and sustained separation between the 2 treatment groups (Figure 1).
- The Kaplan-Meier median PFS was 5.6 months (95% CI: 4.3, 7.8) for sotorasib vs 4.5 months (95% CI: 3.0, 5.7) for docetaxel.

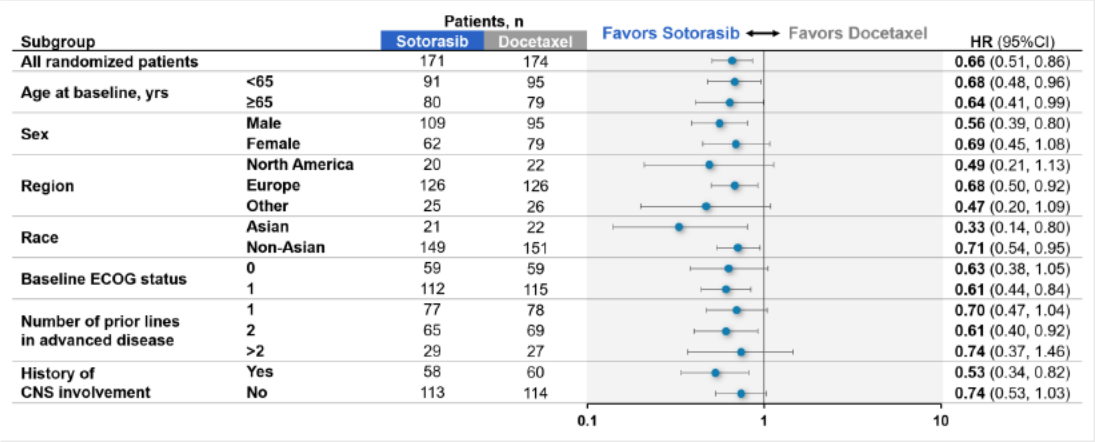
Figure 1. Progression-free Survival Kaplan-Meier Curves as Assessed by the Blinded Independent Central Review Committee (Full Analysis Set) (CodeBreaK 200 Primary Analysis)



Source: Modified from Figure 14-4.1.1 of CodeBreaK 200 Primary Analysis

- More than twice as many patients in the sotorasib group were alive without progression at a 1-year landmark compared with docetaxel (1-year PFS was 24.8% for sotorasib vs 10.1% for docetaxel).
- An alternative measure of treatment effect using Restricted Mean Survival Time (RMST) showed the average PFS time was prolonged by 11.1% (95% CI: 3.3%, 18.9%) for sotorasib vs docetaxel during a 1-year landmark period
- Consistent PFS benefit across subgroups: sotorasib had a consistent PFS benefit across all pre-specified subgroups, including history of central nervous system (CNS) involvement and liver metastasis at baseline (Figure 2).
- Consistent PFS between BICR and investigator assessments: the HR for PFS per investigator assessment was 0.645 (95% CI: 0.504, 0.824).
- The effects of sotorasib on PFS were robust: prespecified sensitivity analyses with alternative censoring rules showed results were consistent with the primary analysis (Section 5.1.5.1). Additional sensitivity analyses addressing several observations in the PFS primary analysis, including scan intervals, differentiated incidence of patients who were randomized but not treated, and potential effects of early censoring confirmed the PFS effect (Section 5.1.5.2).

Figure 2. Forest Plot of Key Subgroup Analyses of Progression-free Survival as Assessed by the Blinded Independent Central Review Committee (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)



Subgroup		Sotorasib	Docetaxel	HR (95%CI)
All randomized patients		171	174	**0.66** (0.51, 0.86)
Age at baseline, yrs	<65	91	95	**0.68** (0.48, 0.96)
	≥65	80	79	**0.64** (0.41, 0.99)
Sex	Male	109	95	**0.56** (0.39, 0.80)
	Female	62	79	**0.69** (0.45, 1.08)
Region	North America	20	22	**0.49** (0.21, 1.13)
	Europe	126	126	**0.68** (0.50, 0.92)
	Other	25	26	**0.47** (0.20, 1.09)
Race	Asian	21	22	**0.33** (0.14, 0.80)
	Non-Asian	149	151	**0.71** (0.54, 0.95)
Baseline ECOG status	0	59	59	**0.63** (0.38, 1.05)
	1	112	115	**0.61** (0.44, 0.84)
Number of prior lines in advanced disease	1	77	78	**0.70** (0.47, 1.04)
	2	65	69	**0.61** (0.40, 0.92)
	>2	29	27	**0.74** (0.37, 1.46)
History of CNS involvement	Yes	58	60	**0.53** (0.34, 0.82)
	No	113	114	**0.74** (0.53, 1.03)

Source: Modified from Figure 14-4.1.5 of CodeBreaK 200 Primary Analysis

Efficacy Results: Secondary Endpoints

- Sotorasib significantly improved ORR (28.1%; 95% CI: 21.5, 35.4) vs docetaxel (13.2%; 95% CI: 8.6,19.2) ($p < 0.001$), confirming the ORR benefit measured in the CodeBreaK 100 phase 2 study that supported the original marketing application and the accelerated approval. The ORR benefit seen in CodeBreaK 200 was consistent across all prespecified subgroups.
- Responses to sotorasib were more durable: the median DOR was 8.6 months (95% CI: 7.1, 18.0) for patients in the sotorasib group vs 6.8 months (95% CI: 4.3, 8.3) for patients in the docetaxel group.
- Sotorasib led to higher disease control rate (DCR): 82.5% for sotorasib vs 60.3% for docetaxel.
- Responses to sotorasib were rapid: the time to response (TTR) among the patients in the sotorasib group was half of that for patients in the docetaxel group (median of 1.4 vs 2.8 months, respectively).
- The overall survival (OS) was not significantly different between treatment groups (median of 10.64 months (95% CI: 8.94, 13.96) in the sotorasib group vs 11.30 months (95% CI: 9.00, 14.85) in the docetaxel group (HR = 1.010; 95% CI: 0.766, 1.331; $p = 0.94$). The updated OS at the time of the 90-day safety update was HR = 0.957 (95% CI: 0.741, 1.235), suggesting no detrimental effect on survival.
- Patient-reported outcome assessments showed that sotorasib provided clinically meaningful stabilization of QoL measures, and delayed time to deterioration for global health status, physical functioning, dyspnea, and cough as compared with docetaxel. Patients in the sotorasib group were also less severely bothered by side effects than those in the docetaxel group.

Efficacy Results: Exploratory Endpoints

- Sotorasib lengthened the median time to progression of CNS disease per Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) vs docetaxel among the 118 patients (58 in sotorasib; 60 in docetaxel) who had prior CNS disease (15.8 months vs 10.5 months, HR = 0.52, 95% CI: 0.26, 1.04).

- Sotorasib lengthened median time to progression of CNS disease per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria vs docetaxel among the 69 patients (40 in sotorasib; 29 in docetaxel) who had stable/treated CNS lesions at baseline: 11.6 months vs 6.0 months (HR = 0.63, 95% CI: 0.25, 1.62) (Dingemans et al, 2023).
- Sotorasib lengthened the median time to progression of CNS disease or all-cause death per RANO-BM criteria vs docetaxel among patients who had stable/treated CNS lesions at baseline: 9.6 months vs 4.5 months (HR = 0.53, 95% CI: 0.28, 1.03) (Dingemans et al, 2023).

Supporting Study CodeBreaK 100 phase 2 Part B (Dose Comparison Study) Key Efficacy Results:

- The ORR was 32.7% (95% CI: 23.8, 42.6) in the 960 mg sotorasib group compared with 24.8% (95% CI: 16.9, 34.1) in 240 mg sotorasib group.
- Median PFS (95% CI) per BICR was 5.39 (4.17, 6.93) months in the 960 mg group and 5.55 (4.14, 8.31) months in the 240 mg group. The stratified Cox HR for 960 vs 240 mg was 0.950 (95% CI: 0.662, 1.363).
- Median DOR was 13.8 (95% CI: 5.6, not estimable) months for the 34 objective responders in the 960 mg group compared with 12.5 (95% CI: 7.0, not estimable) months for the 26 objective responders in the 240 mg group.
- Overall survival data demonstrate that treatment with 960 mg once daily (QD) sotorasib showed a 1.3-month longer median OS and a 25% reduction in the hazard (rate) of death when compared with 240 mg QD sotorasib (median OS was 13.0 months in the 960 mg group and 11.7 months in the 240 mg group (HR of 0.75, 95%CI: 0.53, 1.07, for 960 vs 240 mg group)

Overall, sotorasib treatment provided a consistent clinical benefit as measured by tumor responses across studies, endpoints, and prespecified subgroups. Multiple sensitivity analyses, both pre-specified and additional, on the primary endpoint of PFS in CodeBreaK 200 demonstrated that this clinical benefit was robust.

Results From CodeBreaK 200 Demonstrated that the Sotorasib Safety Profile is Consistent with the Established Safety Profile and That Risks Can Be Adequately Managed:

- Patients who received sotorasib had a longer duration of treatment than patients who received docetaxel: as of 02 August 2022, for patients in the sotorasib group the median (range) duration of treatment was 20 (0.4, 101) weeks administered over 7 (1, 34) 21-day cycles compared with a median (range) duration of treatment of 12 (3, 101) weeks administered over 4 (1, 33) 21-day cycles for patients in the docetaxel group.
- In this study population with advanced NSCLC, deaths in both treatment groups were primarily reports of disease progression. Overall deaths and treatment-emergent fatal adverse events (excluding deaths related to disease progression) were balanced between the sotorasib and docetaxel groups.
- After exclusion of disease progression events, the incidence of adverse events, including the combined incidence of grade 3 and 4 adverse events, serious adverse events, and incidence of treatment discontinuations due to adverse events were similar between treatment groups. When adjusted for the differential exposure, the incidences of these safety parameters were lower in the sotorasib group than in the

docetaxel group, and this pattern is similar when data are summarized by treatment related adverse events.

- Adverse events leading to dose reduction were lower in the sotorasib group than the docetaxel group (26 patients [15.4%] sotorasib vs 43 patients [28.5%] docetaxel), and dose interruptions due to adverse events were higher in the sotorasib group than the docetaxel group (84 patients [49.7%] sotorasib vs 41 patients [27.2%] docetaxel). This pattern remained consistent when incidence was adjusted for exposure or when summarized by treatment related adverse events.

Overall, the types of adverse events reported in the sotorasib and docetaxel groups were differentiated, and consistent with those previously observed with the individual study treatments, or with events expected to occur in the study population independent of drug exposure:

- In patients receiving sotorasib, diarrhea, nausea and decreased appetite were common adverse events, each occurring in ≥ 20% of patients
- In patients receiving docetaxel, fatigue, diarrhea, nausea, anemia, and alopecia were common adverse events, each occurring in ≥ 20% of patients

Key risks (defined as unfavorable effects that are important from a clinical perspective in terms of their frequency and/or severity) for sotorasib include the following:

- Diarrhea: diarrhea was reported in 41.4% of patients in the sotorasib group: 29 patients (17.2%) had grade 1 diarrhea, 18 patients (10.6%) had grade 2 diarrhea, 23 patients (13.6%) had grade 3 diarrhea and there were no grade 4 or fatal diarrhea events. Diarrhea was the most frequent cause of treatment interruptions and dose modifications for sotorasib, however diarrhea rarely led to treatment discontinuation (< 1% of patients discontinued sotorasib due to diarrhea). The median time to onset of diarrhea was 47.5 days and the median duration of each diarrhea adverse event per patient was 22 days. For patients who interrupted treatment due to diarrhea the median duration of treatment interruption was 9 days. These adverse events were effectively managed through dose interruptions and/or reductions and supportive care (eg, antidiarrheal medications).
- Increases in liver enzymes: hepatic adverse events were reported for 41 patients (24.3%) in the sotorasib group and are characterized by abnormal liver function tests. Grade ≥ 3 hepatic events were reported for 32 patients (18.9%). There were no confirmed reported sequalae of liver failure or fatal events. Median time to onset of hepatic adverse events was 46 days and the median duration of hepatic adverse events was 22 days. For patients who interrupted treatment due to hepatic adverse events, the median duration of treatment interruption was 16 days. Treatment was withdrawn in 8% of patients due to hepatotoxicity. Hepatic events were effectively managed through treatment interruption, dose reductions, and/or steroid administration and events were reported as resolved in the majority of patients.
- Pneumonitis/interstitial lung disease (ILD): pneumonitis/ILD was reported for 4 patients (2.4%) in the sotorasib group and was similar to the incidence in the docetaxel group (2.6%). Two of the 4 events in the sotorasib group were grade 1 to 2 in severity, 1 event was grade 3 and 1 event was grade 5 (fatal). The fatal ILD had cause of death recorded as disease progression. Median time to onset of ILD was 42.5 days and the median duration of events was 53 days. Pneumonitis events were effectively managed with treatment modification and steroids and events resolved in all patients except the fatal case due to disease progression.

Benefit-Risk Assessment: Sotorasib Addresses Unmet Need for Patients With Locally Advanced or Metastatic NSCLC With the *KRAS p.G12C* Mutation

- Most patients will progress on first-line treatment, meaning that there is an unmet need to provide second-line therapies for this serious and life-threatening disease. Sotorasib provides an important and more convenient oral targeted therapy for patients.
- Administration of 960 mg sotorasib results in rapid, durable tumor response rates and consistent PFS benefit across subgroups in the randomized phase 3 confirmatory study CodeBreaK 200.
- The effects of sotorasib on PFS were robust: PFS was consistent between BICR and investigator assessment; pre-specified sensitivity analyses with alternative censoring rules showed results were consistent with the primary analysis; additional sensitivity analyses addressing several observations in the PFS primary analysis, including scan intervals and differentiated randomized-not-treated patient numbers and early censoring, confirmed the PFS effect.
- Consistent efficacy results were obtained in supporting clinical studies. For example, patients who received 960 mg sotorasib in CodeBreaK 100 phase 2 Part B (dose comparison study), achieved an ORR of 32.7% (95% CI: 23.8, 42.6), which is consistent with the ORR in patients who received 960 mg in CodeBreaK 200 (28.1%; 95% CI: 21.5, 35.4), and consistent with the results from CodeBreaK 100 phase 2 part A, that supported the original marketing application (ORR = 36.3% (95% CI: 27.8, 45.4).
- The primary analysis OS results and the updated OS results (with narrower confidence interval) for HR does not suggest a detrimental effect in survival for patients receiving sotorasib vs docetaxel in CodeBreaK 200.
- Results from patient-reported outcome analyses using validated assessment tools suggested that treatment with 960 mg sotorasib provides meaningful benefit on QoL, and patients in the sotorasib group are less severely bothered by side effects of treatment.
- Oral administration of the 960 mg dose (now also available as 3 x 320-mg tablets) provides convenience and flexibility for patients and allows facile dose modifications when needed.
- Risks can be monitored and are manageable through supportive care and dose reductions and/or interruptions as provided in approved labeling.
- The safety of sotorasib has been assessed in 2264 patients in clinical studies (1586 patients in monotherapy and 702 patients in combination therapies) and 5444 patient-years of exposure with sotorasib in the post-marketing setting, all of which have shown that risks remain consistent with the known safety profile.

The consistent demonstration of benefit compared with docetaxel, meaningful improvements in QoL, and manageable safety profile support a favorable benefit-risk assessment for sotorasib in a disease setting with high unmet medical need.

In conclusion, sotorasib provides an important oral targeted therapy option for patients with *KRAS p.G12C*-mutated advanced NSCLC in the second-line therapy setting, and fulfills an unmet need for this serious and life-threatening disease. These data support conversion of accelerated to traditional approval for sotorasib.

2. Rationale for Sotorasib in NSCLC

2.1 Disease Background

Lung cancer is the leading cause of cancer death, with more than 80% of all lung cancer cases classified as NSCLC. Worldwide, lung cancer (small cell and non-small cell) is the second most common cancer overall, with an estimated 2.21 million cases in 2020 (WHO Statistics, 2020). The American Cancer Society estimates that there will be approximately 238 340 new cases of lung cancer in the US alone in 2023 and 127 070 will die from the disease (American Cancer Society, 2023). Advanced NSCLC (stage IIIB and IV) is a serious and life-threatening disease, with a 5-year survival rate of 9.3% (SEER, 2022).

Advanced NSCLC is associated with substantial symptom burden, which negatively affects patients' health-related QoL (Gralla et al, 2015; Hopwood and Stephens, 1995). For patients with lung cancer, the most significant symptoms affecting their daily lives are fatigue, shortness of breath, and chronic pain. Other symptoms include insomnia, anxiety, and depression (US FDA, 2013; Liao et al, 2011; Tishelman et al, 2007; Tishelman et al, 2005; Cooley et al, 2003). Therapy that alleviates symptoms and optimizes well-being without adding toxicity is often prioritized by patients over modest gains in survival (Blackhall et al, 2015; Silvestri et al, 1998).

2.2 Current Therapies and Unmet Need

Real-world evidence studies and published literature showed that patients with advanced NSCLC (including those with tumors containing the *KRAS p.G12C* mutation) had poor treatment outcomes with existing therapies in second-line or later, and their prognosis was poor (Spira et al, 2021). Sotorasib gained accelerated approval in the US on 28 May 2021 and was the first available therapy specifically for treatment of adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy. As of 01 August 2023, sotorasib has been approved for the treatment of NSCLC at a 960 mg daily dose in 52 countries, most with the regulatory requirement to complete a phase 3 clinical study to confirm the clinical benefit. In December 2022, adagrasib, another *KRAS p.G12C* inhibitor, was granted accelerated approval in the US for the same indication as sotorasib (Krazati® prescribing information, 2022).

The American Society for Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and European Society for Medical Oncology treatment guidelines list the checkpoint inhibitors either alone or in combination with platinum-based

chemotherapy, as the recommended first-line treatment in patients with advanced NSCLC who test negative for actionable mutations for which approved therapies exist. Approximately two-thirds of patients treated with these first-line regimens progress in the first year (1-year PFS rates are approximately 30% to 40%; Jassem et al, 2021; Hellmann et al, 2019; Gandhi et al, 2018). For these patients whose cancer progressed after treatment with both a checkpoint inhibitor and platinum-based chemotherapy, chemotherapeutic agents, such as docetaxel, have been the standard of care for over 20 years, while newer targeted agents such as sotorasib and adagrasib have been available under accelerated approval in recent years (NCCN, 2023; Hendriks et al, 2023; ASCO, 2019). Docetaxel may be given as monotherapy or in combination with a VEGF inhibitor such as ramucirumab. Approved second-line or later therapies for previously treated patients with advanced NSCLC and no actionable mutations are summarized in Appendix 1.

2.2.1 Docetaxel

Docetaxel is an antimicrotubule taxane derivative used for treatment of a variety of solid tumors. Docetaxel (administered 75 mg/m^2 IV over 1 hour once every 3 weeks (Q3W) is approved globally as a single agent for the treatment of patients with locally-advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy (Taxotere® prescribing information, 2020). Because docetaxel is considered a standard of care for the treatment of advanced NSCLC in patients who have progressed after checkpoint inhibitor and platinum-based doublet chemotherapy and is regionally widely available, Amgen, in discussion with regulatory agencies, selected docetaxel as the comparator vs sotorasib for the phase 3 confirmatory study, CodeBreaK 200.

Historically, docetaxel has been the preferred treatment option following progression on platinum-based chemotherapy and/or immunotherapy based on ORR of 12% to 14%, median PFS of 2.8 to 4.2 months, and median OS of 7.9 to 9.4 months (Jänne et al, 2017; Borghaei et al, 2015). In a real-world study examining the prognosis of patients with advanced *KRAS p.G12C*-mutated NSCLC who were treated with docetaxel as a second-line therapy, the median OS was 6.2 (range: 4.6 to 7.6) months (Gray et al, 2023).

While docetaxel has benefit as a second-line agent in patients with advanced NSCLC who have platinum-resistant tumors, the toxicity profile of docetaxel when given Q3W is also well established (Engels and Verweij, 2005). The FDA has issued a boxed warning for docetaxel describing risks of “toxic deaths, hepatotoxicity, neutropenia,

hypersensitivity reactions, and fluid retention." The neutropenia and febrile neutropenia associated with IV docetaxel can require hospitalization (Montero et al, 2005), and can occasionally be life-threatening (Powell et al, 2022). Other side effects of docetaxel based on the prescribing information include nausea, vomiting, stomatitis, diarrhea, skin and nail toxicity, peripheral edema, alopecia, anemia, and neuropathy related to cumulative dose (Engels and Verweij, 2005).

Both the incidence and severity of docetaxel-induced adverse events are related to exposure (Kenmotsu and Tanigawara, 2015), and significant inter-individual variability in exposure has been described based on genetic variation and drug-drug interactions that impact docetaxel clearance (Hirth et al, 2000). Docetaxel treatment also led to worse scores in QoL and time to deterioration assessments than biologic therapies such as the immune checkpoint antibodies atezolizumab, pembrolizumab, and nivolumab (Barlesi et al, 2019; Bordoni et al, 2018; Reck et al, 2018; Gralla et al, 2015).

2.2.2 Unmet Need

There is a need for new second-line treatments for patients with NSCLC who have progressed after receiving checkpoint inhibitors and platinum-based chemotherapy, including those patients with *KRAS p.G12C*-mutated NSCLC, a mutation which rarely occurs with other actionable driver mutations (Section 2.3). There are few recommended second line treatment options (Appendix 1). In 1999, docetaxel was approved for use after failure of prior platinum-based chemotherapy based on a demonstrated improvement in survival over best supportive care (Taxotere® prescribing information, 2020). The combination of docetaxel plus ramucirumab, a VEGF inhibitor, has demonstrated a marginal improvement in survival as compared to docetaxel (HR = 0.86, 95% CI: 0.75, 0.98) (Garon et al, 2014) and is used less frequently than docetaxel alone in the US; however, the combination is associated with significant toxicity (serious adverse reactions include febrile neutropenia, pneumonia, and neutropenia; common adverse reactions include neutropenia fatigue/asthenia, and stomatitis/mucosal inflammation [Cyramza® prescribing information, 2020]) and has limited usage globally because it is not approved or reimbursed in many regions. The option to use an checkpoint inhibitor in this setting is limited due to the majority of patients being treated with this therapy in the frontline setting. Given the limited treatment options and challenges associated with docetaxel as standard of care (modest efficacy, serious toxicities, IV route of administration, poor tolerability, and patient preference) in

advanced NSCLC, patients with *KRAS p.G12C*-mutated tumors may benefit from sotorasib oral targeted therapy.

The confirmatory study, CodeBreaK 200, supports the favorable benefit-risk assessment for sotorasib treatment in patients with *KRAS p.G12C*-mutated advanced NSCLC to address this unmet need.

2.3 Oncogenic RAS and *KRAS p.G12C* Mutations

Several proto-oncogene mutations have been implicated in the development of NSCLC. Among these, mutations in the rat sarcoma viral oncogene homolog (*RAS*) family of proto-oncogenes are among the most prevalent. The *RAS* family of proto-oncogenes consists of 3 closely related genes that encode guanosine triphosphatases (GTPases) responsible for regulating cellular proliferation and survival (Simanshu et al, 2017; Barbacid, 1987). Different tumor types are associated with mutations in certain isoforms of *RAS*, with *KRAS* oncogene homolog being the most frequently mutated isoform in most cancers (Prior et al, 2012).

Of the *KRAS* mutations, an estimated 80% occur at codon 12. The *KRAS p.G12C* mutation in codon 12 is a single guanine to thymine substitution that results in a glycine to cysteine substitution at amino acid position 12. This structural change in the protein results in a defect in the association of guanosine triphosphatase-activating proteins, thereby reducing the hydrolysis of guanosine triphosphate (GTP) by the KRAS protein. The resulting accumulation of active, GTP-bound KRAS leads to aberrant proliferative and survival signaling in tumor cells (Jones et al, 2017). These KRAS oncogenic mutations were considered “undruggable” (Cui et al, 2020) for decades (McCormick, 2016), but discovery of a cryptic pocket in KRAS enabled relatively specific inhibitors to be developed, providing structure-based validation that KRAS is targetable (Ostrem et al, 2013). The *KRAS p.G12C* mutation rarely occurs (≤ 1.2%) with other actionable drivers (eg, *EGFR* mutation, *ALK* rearrangement, *ROS1* rearrangement, and *BRAF* mutation), but was observed in the presence of higher frequency of serine/threonine kinase 11 mutation, higher expression levels of programmed death-ligand 1 (PD-L1), and higher tumor mutational burden (Spira et al, 2021). This means that targeted therapies approved prior to sotorasib are not an option for most patients with *KRAS p.G12C* mutations (Section 2.2.2).

It is estimated that the *KRAS p.G12C* mutation is present in approximately 12% to 14% of NSCLC adenocarcimoas in Western regions, and approximately 3% of all NSCLC in Asia (Lee et al, 2022; Liu et al, 2020; Biernacka et al, 2016) and it has been identified as

a putative oncogenic driver in this tumor type (American Association for Cancer Research Project GENIE Consortium, 2017; Biernacka et al, 2016; Fernández-Medarde and Santos, 2011). Based on the estimated prevalence of the *KRAS p.G12C* mutation in NSCLC and the estimated number of worldwide lung cancer cases in 2020 (NSCLC comprising approximately 85% of lung cancer), the estimated number of new cases diagnosed annually for *KRAS p.*G12C-mutated NSCLC is approximately 28 000 in North America, 53 000 in Europe, and 33 000 in Asia.

2.4 Sotorasib in Advanced NSCLC

Sotorasib was developed to fulfill an unmet medical need to provide a targeted therapy for patients with previously treated locally advanced/metastatic NSCLC with the *KRAS p.G12C* mutation. The first approval of sotorasib 960 mg once daily (QD) was in the US for the treatment of adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least 1prior systemic therapy.

2.5 Sotorasib Mechanism of Action

Sotorasib is a small molecule inhibitor that covalently and selectively binds to the $KRAS^{G12C}$ mutant protein and locks it in a guanosine diphosphate-bound, inactive state. This blocks the interaction of $KRAS^{G12C}$ with effectors thereby preventing downstream MAPK pathway signaling (Canon et al, 2019; Simanshu et al, 2017; Ostrem et al, 2013).

2.6 Sotorasib Tablet Strengths

At the time of accelerated approval, sotorasib was available as a 120 mg tablet, meaning the 960 mg dose was administered orally as 8 tablets QD. As of 20 January 2023, sotorasib is also available in a 320 mg tablet strength, reducing the pill burden to 3 tablets QD.

3. Regulatory History

3.1 Sotorasib Accelerated Approval in NSCLC

As of 01 August 2023, sotorasib is authorized in 52 countries for treatment of adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy. In these countries, sotorasib is approved under the proprietary name LUMAKRAS® or LUMYKRAS® (960 mg QD).

The original marketing authorization for the above indication was granted under conditional or traditional/full approval in several countries, based primarily upon results demonstrating a favorable benefit-risk assessment for sotorasib from the pivotal,

phase 2, open-label, single-group study (CodeBreaK 100) that included patients with locally advanced or metastatic NSCLC with *KRAS p.G12C* mutation.

The original registrational study data package included 427 patients treated with sotorasib monotherapy across all doses and tumor types in the ongoing phase 1 and phase 2 portions of CodeBreaK 100. This included 357 patients who were treated with 960 mg QD sotorasib for all tumor types, of whom 204 patients had NSCLC.

In the original pivotal study, the phase 2 part A portion of CodeBreaK 100, total of 124 patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC (hereafter referred to as NSCLC) were enrolled, received ≥ 1 dose of sotorasib monotherapy 960 mg, had ≥ 1 measurable lesion (based on blinded central review) at baseline, and were included in the full analysis set for efficacy assessments. These 124 patients had a BICR-assessed ORR of 36.3% (95% CI: 27.8, 45.4) and median duration of response (DOR) of 10 months (range: 1.3+, 11.1).

Most patients with NSCLC who received 960 mg QD sotorasib monotherapy (201 of 204 patients [98.5%]) had ≥ 1 treatment-emergent adverse event (hereafter referred to as adverse event) during the study. Of these, 120 patients (58.8%) had adverse events ≥ grade 3 in severity. Serious adverse events were reported for 103 patients (50.5%). Adverse events leading to reduction/interruption or discontinuation of sotorasib monotherapy were reported for 71 patients (34.8%) and 19 patients (9.3%), respectively. Thirty-two patients (15.7%) had fatal adverse events; none of the deaths were considered by the investigator as related to sotorasib treatment. The most common adverse drug reactions (ADRs) with sotorasib use (≥ 20%) were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. The most common laboratory abnormalities (≥ 25%) were decreased lymphocytes, decreased hemoglobin, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased calcium, increased alkaline phosphatase, increased urine protein, and decreased sodium (Lumakras® prescribing information, 2023).

These data supporting the accelerated approval of sotorasib monotherapy demonstrated a clinically meaningful and durable objective response among patients with advanced NSCLC with a manageable safety profile. In the US, accelerated approval of sotorasib was granted on 28 May 2021, marking the first approval of a *KRAS p.G12C* inhibitor.

3.2 Supplemental NDA (Confirmatory Study)

To support conversion to traditional approval and to fulfill a postmarketing requirement, Amgen submitted a supplemental new drug application (sNDA) 214665/S-005 on 24 February 2023. The sNDA included results from the confirmatory phase 3 study (CodeBreaK 200) and a dose comparison study (CodeBreaK 100 phase 2 Part B). A 90-day safety update for the sNDA providing updated safety data and efficacy data for patients with NSCLC in these 2 studies was submitted in May 2023.

CodeBreaK 200 is an ongoing, phase 3, multicenter, randomized, open-label, active-controlled study of sotorasib compared with docetaxel for the treatment of previously treated locally advanced and unresectable or metastatic *KRAS p.G12C*-mutated NSCLC. The purpose of CodeBreaK 200 was to provide confirmatory clinical data to support traditional approval. Enrollment into this study is complete, with 345 patients enrolled. Analysis of results of the efficacy and safety data from these patients is provided in Section 5.1 and Section 6.1, respectively. As of the date of this briefing document, sotorasib is the only *KRAS p.G12C* inhibitor with positive phase 3 data from a large, randomized study in advanced NSCLC.

CodeBreaK 200 was designed in consultation with multiple national health authorities, including FDA. In the original design, agreement with FDA was reached on the open-label study design, patient population, sample size, comparator (docetaxel), statistical analysis methods and testing strategy (primary endpoint [PFS per RECIST 1.1 as assessed by BICR] and key secondary endpoints [OS and ORR]), and overall approach to measure patient-reported outcomes (PROs). CodeBreaK 200 was initiated prior to the primary analysis of the phase 2 study.

Upon primary analysis of the phase 2 part A portion of CodeBreaK 100 in which sotorasib demonstrated an ORR of 36.3% (95% CI: 27.8, 45.4) and a DOR of 10 months (range 1.3+, 11.1), the FDA recommended changes to CodeBreaK 200 in order to maximize the number of patients who received sotorasib. The following key changes were made to the study:

- change in sample size based on powering for PFS only but not the secondary endpoint of OS (resulting in a reduction of planned sample size from 650 to 330 patients).
- addition of an interim analysis for efficacy to enable early stopping
- allowance of crossover from docetaxel to sotorasib treatment at documented disease progression (not allowed in original protocol design and implemented when 236 patients were already enrolled)

A summary of key regulatory interactions with the FDA including these agreed study design changes is shown in Table 1.

Table 1. Summary of Key Regulatory Interactions with FDA and Correspondence Pertaining to CodeBreaK 200

Date	Regulatory Interaction/Milestone
05 November 2019	Type B (pre-IND/pre-phase 3) interactions to reach agreement on the design of the proposed phase 3 confirmatory study CodeBreaK 200 (Study 20190009). FDA agreed with the overall design of the study, including the open-label design, patient population, sample size, comparator (docetaxel), statistical analysis methods and testing strategy (primary endpoint [PFS per RECIST 1.1 as assessed by BICR] and key secondary endpoints [OS and ORR]), and overall approach to measure PROs.
04 June 2020	First patient was enrolled in CodeBreaK 200.
05 August 2020	Sotorasib was granted fast track designation for the treatment of metastatic NSCLC with *KRAS p.G12C* mutation with disease progression on or after platinum-based chemotherapy
10 November 2020	Type B pre-NDA Meeting Minutes. Regarding confirmatory study CodeBreaK 200, FDA suggested an early stopping rule for futility in the docetaxel group and/or a 2:1 randomization scheme to maximize the number of patients with *KRAS p.G12C*-mutated NSCLC who receive sotorasib. Amgen provided details regarding the independent DMC for CodeBreaK 200. The Agency acknowledged Amgen's response describing an early analysis for futility, and that the clinical trial was already undergoing enrollment.
07 December 2020	Sotorasib was granted breakthrough therapy designation by FDA for treatment of patients with locally advanced or metastatic NSCLC with *KRAS p.G12C* mutation, as determined by an FDA-approved test, following at least 1 prior systemic therapy.
08 December 2020	FDA issued an information request regarding CodeBreaK 200 and recommended revisions to the study design to reduce the number of patients required for enrollment (sample size calculation based on powering for PFS only, allowance of cross over from the docetaxel group at progression, IA for efficacy, consideration of 2:1 randomization).
16 December 2020	Sotorasib original NDA 214665 submitted for accelerated approval.
09 February 2021	Type B Meeting to obtain the Agency's formal advice and discuss Amgen's proposal for the revised design of CodeBreaK 200 based on FDA recommendations. FDA agreed to the proposed revisions to the study design and statistical analysis plan including the decreased sample size such that the study was powered for the primary endpoint of PFS but not the secondary endpoint of OS, plan for interim analysis of PFS at 70% of events, and allowance of cross over from docetaxel group to sotorasib.

Date	Regulatory Interaction/Milestone
17 February 2021	Amgen submitted protocol Amendment 3 for CodeBreaK 200 based on the Type B Meeting outcomes. Key changes agreed by Amgen and FDA included the following: • revision of the sample size (n) based on PFS endpoint only (from n = 650 to n = 330) • incorporation of PFS IA at approximately 70% information fraction when approximately 160 PFS events were observed from both treatment groups • allowance of patients enrolled in the docetaxel group to crossover to the sotorasib group upon centrally-confirmed disease progression that had been confirmed by BICR or if early efficacy of the study was noted by the DMC at the PFS interim analysis
26 April 2021	CodeBreaK 200 completed enrollment.
28 May 2021	Amgen received FDA accelerated approval letter for sotorasib for treatment of adult patients with *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least 1 prior systemic therapy.
05 May 2022	Ad hoc meeting to discuss results of interim analysis and procedural issue identified by imaging vendor. FDA recommended continuing the study to PA and further recommended a global re-read of all scans.
21 October 2022	Type B pre-sNDA meeting held with FDA. FDA and Amgen reached agreement on the adequacy of the clinical data package for the filing, as well as agreement on updates to the structure and format of the filing and plans for rolling review.
24 February 2023	Submission of sNDA 214665/S-005 which provided phase 3 confirmatory data from CodeBreaK 200, as well as data from CodeBreaK 100 phase 2 Part B (dose comparison) for conversion to traditional approval for the proposed indication, as well as fulfillment of postmarketing requirements.

Page 2 of 2

BICR = blinded independent central review; DMC = data monitoring committee; FDA = Food and Drug Administration; IA = interim analysis; IND = Investigational New Drug; *KRAS p.G12C* = KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level; NDA = New Drug Application; NSCLC = non-small cell lung cancer; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; RECIST = response evaluation criteria in solid tumors; sNDA = supplemental New Drug Application

4. Clinical Development Program

The key studies included in the sNDA are as follows:

CodeBreaK 200 (Study 20190009): an ongoing, phase 3, open-label study evaluating the efficacy, safety, tolerability, and pharmacokinetics (PK) of sotorasib in comparison with docetaxel in patients with previously treated *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC.

CodeBreaK 100 phase 2 Part B (Study 20170543): a randomized substudy of an ongoing, phase 1/2, open-label study evaluating the safety, tolerability, PK, pharmacodynamics, and efficacy of sotorasib in patients with *KRAS p.G12C*-mutated NSCLC, colorectal cancer (CRC), and other solid tumor types. The goal of the phase 2 Part B substudy is to evaluate the safety and efficacy of sotorasib as monotherapy at 960 mg QD and 240 mg QD in patients with NSCLC.

Further details on these studies are provided in Table 2.

Table 2. Key Clinical Studies Supporting the Supplemental Marketing Application

Study No./NCT No. (Study Status)[a] [link to results]	Study Design	Investigational Products; Dosage Regimens; Route of Administration	Study Objectives or Endpoints	No. of Patients Enrolled (Actual/Planned)	Key Entry Criteria	No. of Centers and Countries[b]
20190009/NCT04303780 (Ongoing) [efficacy data summarized in Section 5.1; safety data summarized in Section 6.1]	Phase 3 multicenter, randomized, open-label, active-controlled	sotorasib 960 mg PO QD docetaxel 75 mg/m^2 IV Q3W	efficacy, safety, tolerability, PROs, PK	Planned: 165 sotorasib 165 docetaxel Enrolled: 345 (171 sotorasib; 174 docetaxel)	men or women ≥ 18 years of age with previously treated advanced NSCLC with *KRAS p.G12C* mutation (and no other known oncogenic driver mutation for which there is an approved targeted therapy)	148 centers 22 countries

Page 1 of 2

Footnotes are on the last page of this table

Table 2. Key Clinical Studies Supporting the Supplemental Marketing Application

Study No./NCT No. (Study Status)[a] [link to results, if applicable]	Study Design	Investigational Products; Dosage Regimens; Route of Administration	Study Objectives or Endpoints	No. of Patients Enrolled (Actual/Planned)	Key Entry Criteria	No. of Centers and Countries[b]
20170543/NCT03600883 (Ongoing)[c]	Phase 1/2, monotherapy and in combination, nonrandomized, open-label, dose exploration	oral doses of sotorasib (monotherapy treatment groups only)[c]	safety, tolerability, efficacy, PK, PD	Phase 1 222/245 Phase 2: Part A: 260/310 Part B: 209/200	men or women ≥ 18 years of age with previously treated advanced solid tumors with *KRAS p.G12C* mutation	115 centers 16 countries
Phase 2 Part A (pivotal) [data summarized in Section 3.1]		960 mg sotorasib PO (recommended phase 2 dose)	safety, tolerability, efficacy, PK, PD, PRO			
Phase 2 Part B (dose comparison) efficacy data summarized in Section 5.2.2; safety data summarized in Section 6.2]		960 mg or 240 mg sotorasib PO QD	safety, tolerability, efficacy, PK, PD, PRO	240 mg: 105/100 960 mg: 104/100		

Page 2 of 2

IV = intravenous; *RAS p.G12C* = KRAS gene with a mutation resulting in a G12C amino acid substitution at the protein level; NSCLC = non-small cell lung cancer; PD = pharmacodynamics; PK = pharmacokinetics; PO = administered orally; PRO = patient-reported outcome; QD = once daily; Q3W = every 3 weeks

[a] Status as of 09 September 2022 for CodeBreaK 100 phase 2 part B and 02 August 2022 for remaining studies.

[b] Number of patients contributing data included in the analysis.

[c] Other parts of CodeBreaK 100 include phase 1 part 1a, 1b, 1d, and part 2a, 2b, 2d and 2e which studied different doses of sotorasib with and without food Other Studies (used in an integrated analysis of pooled sotorasib monotherapy data to support Section 6.2, Safety); studies included in the integrated safety analysis (sotorasib monotherapy; pooled data) were Studies 20190009, 20170543, 20190147, and 20190135 (Subprotocol G).

5. Efficacy

The efficacy of sotorasib for the treatment of patients with *KRAS p.G12C*-mutated advanced NSCLC is primarily demonstrated by the following results:

- Efficacy results from the phase 2 portion of CodeBreaK 100 (Part A) included in the original marketing application, which were the primary support for the original accelerated approval of sotorasib (Section 3.1).
- Efficacy results from the confirmatory phase 3 study (CodeBreaK 200), which were included in a supplemental marketing application and 90-day efficacy update to support conversion to traditional approval (Section 5.1).
- Supporting efficacy results from CodeBreaK 100 phase 2 Part B, which was a dose comparison study (Section 5.2.1).

5.1 Phase 3 Confirmatory Study CodeBreaK 200

5.1.1 Study Design

CodeBreaK 200 is an ongoing, phase 3, multicenter, randomized, open-label, active-controlled study to evaluate the efficacy, safety, and tolerability of sotorasib vs docetaxel in patients with previously treated, locally advanced and unresectable or metastatic NSCLC with the *KRAS p.G12C* mutation (Figure 3).

The primary objective of CodeBreaK 200 is to compare the efficacy of sotorasib vs docetaxel, as assessed using PFS as the primary endpoint by BICR per RECIST v1.1, in previously treated patients with *KRAS p.G12C*-mutated NSCLC. Secondary objectives were classified prospectively as either “Key” or “Other” as follows:

Key Secondary Objectives

- to compare the efficacy of sotorasib vs docetaxel as assessed by
  - OS
  - ORR
- to compare PROs as assessed by
  - QLQ-LC13
  - QLQ-C30

Other Secondary Objectives

- to compare the efficacy of sotorasib vs docetaxel as assessed by DOR, time to response (TTR), and DCR
- to compare the safety and tolerability of sotorasib vs docetaxel
- to compare the effect of treatment with sotorasib on other treatment- and disease-related symptoms and health-related QoL relative to docetaxel
- to characterize the PK of sotorasib and its major metabolites

Exploratory objectives were to compare efficacy of sotorasib vs docetaxel as assessed by a second PFS analysis (progression-free survival 2 [PFS2]; defined as time from randomization to second progression or disease progression on next-line of treatment,

based on investigator assessment) and time to progression of CNS disease for the subset of patients who had prior CNS disease at study entry. The corresponding endpoints for these secondary and exploratory objectives are listed in Table 31 of Appendix 2.

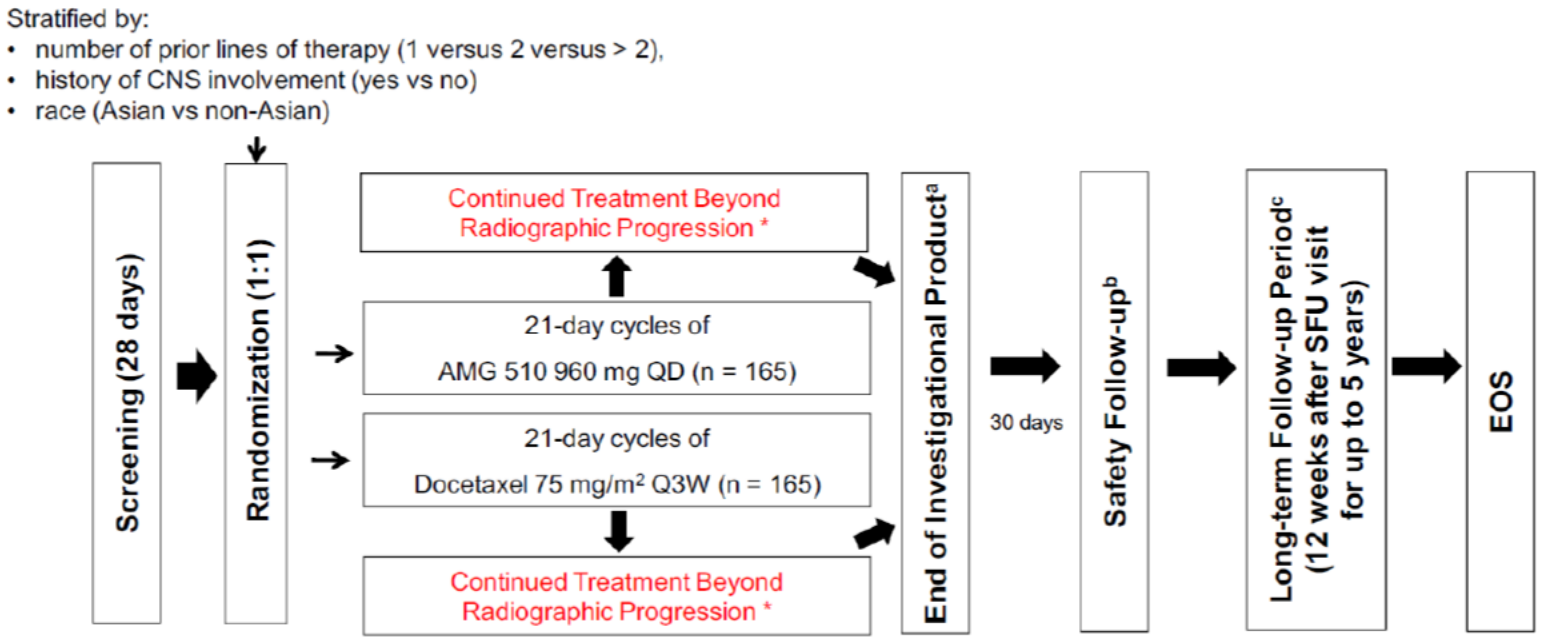
CodeBreaK 200 includes 4 periods: a screening period, during which patients must have documentation of the *KRAS p.G12C* mutation identified by central laboratory testing with the Qiagen KRAS *therascreen*® KRAS RGQ polymerase chain reaction Kit, a treatment period, a safety follow-up period of 30 days after the end of the last dosing interval, and a long-term follow-up period (Figure 3).

Once a patient was determined to have radiological progression by the investigator and their progressive disease was confirmed by independent central review, they were given the opportunity to either:

- continue to receive investigational product (for patients in both groups), or
- to crossover and receive sotorasib (for patients in the docetaxel group only).

The treatment effect assumption for median PFS and median OS in the docetaxel group was 5 months (Charpidou et al, 2019) and 9 months (Borghaei et al, 2015; Garon et al, 2014), respectively. The sample size was determined to achieve 90% power to detect a PFS HR of 0.65 with approximately 230 PFS events. The study is not powered for OS. The OS primary analysis was planned to occur at approximately 198 OS events (approximately 60% maturity). It was estimated to have approximately 96% probability to observe a HR < 1 when the true OS HR is 0.75.

Figure 3. Study Schema (CodeBreaK 200)



CNS = central nervous system; EOS = End of Study; QD = once a day; Q3W = every 3 weeks; SFU = safety follow-up

[a] Treatment with investigational product continued until independent central confirmation of progression, intolerance of treatment, initiation of another anticancer therapy, withdrawal of consent, or death. Patients who consent to treatment beyond progression or to crossover from docetaxel to sotorasib continued to receive investigational product after independent central confirmation of progression at the time of first progressive disease.

[b] Upon permanent discontinuation from the study treatment for any reason, a SFU visit was conducted 30 days (± 7 days) after the end of the last dosing interval of investigational product.

[*c] Details regarding imaging assessments post-treatment period, treatment beyond radiograph progression, and crossover from docetaxel are detailed in the protocol. The protocol for Study 20190009 (originally dated 19 November 2019) was amended 4 times as of the date of this briefing document.

Source: Figure 8-1 of CodeBreaK 200 Primary Analysis

5.1.2 Efficacy Analyses

The efficacy analyses of primary endpoint and key secondary endpoints to compare sotorasib vs docetaxel were conducted on the full analysis set (intention-to-treat [ITT] population). The primary analysis of PFS was based on BICR assessed outcomes. The timing for the primary analysis of PFS was event driven and was to occur when approximately 230 PFS events were reached cumulatively in the 2 treatment groups. A multiplicity adjusted graphical approach was applied for testing the endpoints of PFS, OS, and ORR (Maurer and Bretz, 2013).

One interim analysis for PFS was planned when approximately 70% (160 events cumulatively) of the target PFS events were observed from both groups, or when the enrollment was finished and the last patient randomized had the opportunity to have 6 weeks of follow-up, whichever occurred later. The monitoring boundary for early stopping for efficacy was based on an O'Brien Fleming type alpha spending function for multiplicity adjustment. The actual information fraction was calculated based on the number of observed events at the time of the analysis. As designed and regardless of the OS analysis result at the planned PFS primary analysis, the study would not terminate at PFS analyses and patients would continue to be followed for OS data until the targeted number of death events are reached, to enable analyses of OS and a robust description of the totality of the data. A review of the interim analysis data by the Data Monitoring Committee (DMC) resulted in a decision to continue the study to primary analysis. The data cutoff for the PFS primary analysis was 02 August 2022. As of this data cutoff, 223 PFS events were observed. The pre-specified statistical methods for the primary and secondary efficacy endpoints are summarized below and provided in more detail for all endpoints in Appendix 2.

- Distribution of PFS and OS were estimated using the Kaplan-Meier method. The HR and its 95% CI were estimated using a Cox proportional hazards model stratified by the randomization stratification factors. The inferential comparison was made using a stratified log rank test.
- ORR was calculated, and the associated 95% CI were estimated using the Clopper-Pearson method. The inferential comparison for ORR was made using the Cochran-Mantel-Haenszel chi-square test controlling for the randomization stratification factors.

5.1.2.1 Statistical Hierarchy of Endpoints

As prespecified in the statistical analysis plan (SAP), formal statistical testing was conducted for PFS primary endpoint and secondary endpoints (OS and ORR) following the graphical multiple testing procedure of Maurer and Bretz, 2013 to control the

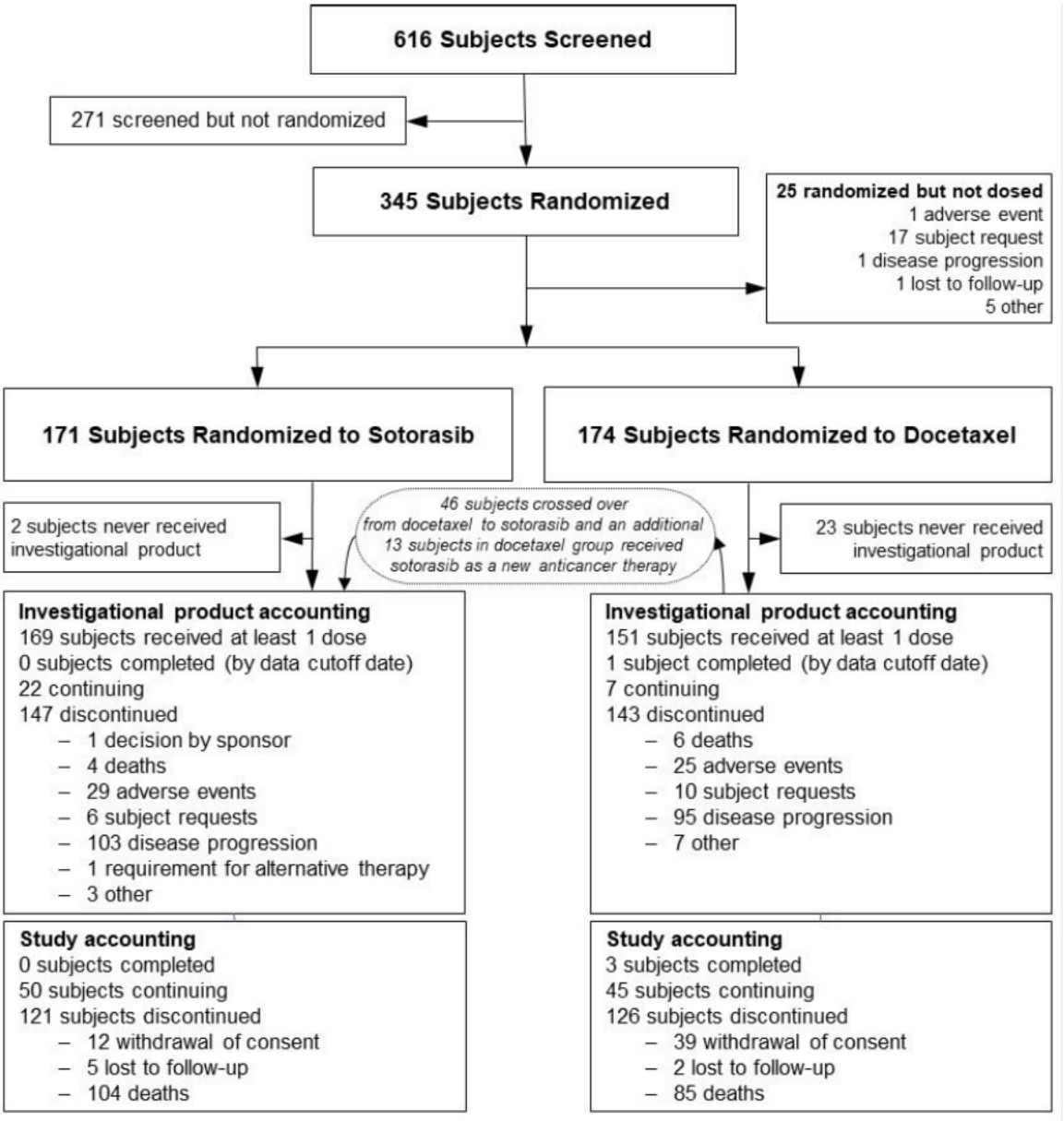
study-level overall type I error rate below 2-sided 0.05 level. Starting with PFS, if the hypothesis of PFS was rejected, ORR would be tested using 2-sided 0.01 level. With the rejection of ORR hypothesis, OS would be tested using 2-sided 0.05 level. If ORR hypothesis failed to be rejected, OS would be tested using 0.04 level. With the rejection of OS hypothesis, ORR could be retested using 2-sided full 0.05 level. If all 3 hypotheses of PFS, OS, ORR were rejected, key PRO secondary endpoints would be tested using Holm's procedure.

5.1.3 Patient Disposition

The full analysis set (ITT population) included all randomized patients (N = 345 patients [171 sotorasib, 174 docetaxel]); data were analyzed according to randomized treatment assignment. As specified in the SAP, patients who were randomized but did not receive treatment (hereafter referred to as randomized-not-treated patients) were included in the efficacy summary based on the ITT population. As of the data cutoff date of 02 August 2022, 320 patients (92.8%) received at least 1 dose of investigational product (169 [98.8%] sotorasib, 151 [86.8%] docetaxel) and comprise the safety analysis set. Patient disposition is shown in Figure 4.

During the study, 46 patients who were randomized to docetaxel crossed over to sotorasib treatment following centrally-confirmed progressive disease (referred to as "crossover patients"). As of the data cutoff date of 02 August 2022, 34 crossover patients (73.9%) discontinued investigational product for the following reasons: disease progression (26 patients [56.5%]); adverse event (3 patients [6.5%]); death (2 patients [4.3%]); other (2 patients [4.3%]); patient request (1 patient [2.2%]). Of the 21 crossover patients (45.7%) who discontinued the study, 17 patients (37.0%) died, and 4 patients (8.7%) withdrew consent.

Figure 4. Patient Disposition for CodeBreaK 200 (Enrolled Patients) (CodeBreaK 200 PFS Primary Analysis)



Source: Modified from Table 14-1.1.1, Table 14-1.1.2, and Table 14-8.1.502 of CodeBreaK 200 Primary Analysis

5.1.4 Baseline Demographics and Key Baseline Characteristics

The majority of patients in the study were men (204 patients [59.1%]), White (286 patients [82.9%]) or Asian (43 patients [12.5%]), and not Hispanic/Latino (328 patients [95.1%]). The median (range) age was 64.0 (32 to 88) years, and approximately half of patients were < 65 years (186 patients [53.9%]).

No noteworthy differences in baseline demographics or baseline characteristics were observed between the treatment groups (Table 3 and Table 4).

**Table 3. Baseline Demographics (Full Analysis Set)
(CodeBreaK 200 PFS Primary Analysis)**

	Sotorasib (N = 171)	Docetaxel (N = 174)	Total (N = 345)
Age at randomization (years)			
n	171	174	345
Mean	63.4	63.6	63.5
SD	9.9	9.1	9.5
Median	64.0	64.0	64.0
Min, Max	32, 88	35, 87	32, 88
Age group 1 - n (%)			
< 65 years	91 (53.2)	95 (54.6)	186 (53.9)
≥ 65 years	80 (46.8)	79 (45.4)	159 (46.1)
Age group 2 - n (%)			
18 - 64 years	91 (53.2)	95 (54.6)	186 (53.9)
65 - 74 years	58 (33.9)	58 (33.3)	116 (33.6)
75 - 84 years	20 (11.7)	20 (11.5)	40 (11.6)
≥ 85 years	2 (1.2)	1 (0.6)	3 (0.9)
Sex - n (%)			
Male	109 (63.7)	95 (54.6)	204 (59.1)
Female	62 (36.3)	79 (45.4)	141 (40.9)
Ethnicity - n (%)			
Hispanic/Latino	5 (2.9)	9 (5.2)	14 (4.1)
Not Hispanic/Latino	165 (96.5)	163 (93.7)	328 (95.1)
Unknown	1 (0.6)	2 (1.1)	3 (0.9)
Race - n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	21 (12.3)	22 (12.6)	43 (12.5)
Black or African American	2 (1.2)	0 (0.0)	2 (0.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	142 (83.0)	144 (82.8)	286 (82.9)
Multiple	1 (0.6)	0 (0.0)	1 (0.3)
Other	4 (2.3)	7 (4.0)	11 (3.2)
Unknown	1 (0.6)	1 (0.6)	2 (0.6)

N = number of patients in the analysis set; n = number of patients with observed data;
Notes: Data cut-off date = 02 August 2022
The patient with "Multiple" race has listed "White" as primary race (1) in case report form, thus is considered under "White" in the by race subgroup analysis.
Source: Modified from Table 14-2.1.1 of CodeBreaK 200 Primary Analysis

Table 4. Key Baseline Characteristics (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

	Sotorasib (N = 171)	Docetaxel (N = 174)	Total (N = 345)
ECOG performance status (screening) - n (%)			
0	59 (34.5)	59 (33.9)	118 (34.2)
1	112 (65.5)	115 (66.1)	227 (65.8)
Prior line of therapy[a,b] - n (%)			
First	171 (100.0)	174 (100.0)	345 (100.0)
Second	97 (56.7)	100 (57.5)	197 (57.1)
Third	29 (17.0)	27 (15.5)	56 (16.2)
Fourth	6 (3.5)	6 (3.4)	12 (3.5)
Fifth	2 (1.2)	2 (1.1)	4 (1.2)
Sixth	0 (0.0)	1 (0.6)	1 (0.3)
Seventh	0 (0.0)	0 (0.0)	0 (0.0)
Maintenance	62 (36.3)	56 (32.2)	118 (34.2)
Other	2 (1.2)	2 (1.1)	4 (1.2)
Number of complete prior lines of therapy[b] - n (%)			
1	74 (43.3)	74 (42.5)	148 (42.9)
2	68 (39.8)	73 (42.0)	141 (40.9)
> 2	29 (17.0)	27 (15.5)	56 (16.2)
Number of advance prior lines of therapy[c] - n (%)			
1	77 (45.0)	78 (44.8)	155 (44.9)
2	65 (38.0)	69 (39.7)	134 (38.8)
> 2	29 (17.0)	27 (15.5)	56 (16.2)
History of CNS involvement - n (%)			
Yes	58 (33.9)	60 (34.5)	118 (34.2)
No	113 (66.1)	114 (65.5)	227 (65.8)
Liver metastasis - n (%)			
Yes	30 (17.5)	35 (20.1)	65 (18.8)
No	141 (82.5)	139 (79.9)	280 (81.2)
Smoking history (tobacco) - n (%)			
Never	5 (2.9)	8 (4.6)	13 (3.8)
Current	32 (18.7)	35 (20.1)	67 (19.4)
Former	134 (78.4)	131 (75.3)	265 (76.8)
Histology - n (%)			
Squamous	1 (0.6)	7 (4.0)	8 (2.3)
Non-squamous	169 (98.8)	165 (94.8)	334 (96.8)
Other	1 (0.6)	2 (1.1)	3 (0.9)
Disease stage - n (%)			
Locally advanced and unresectable	9 (5.3)	8 (4.6)	17 (4.9)
Metastatic	162 (94.7)	166 (95.4)	328 (95.1)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)

Page 1 of 2

Footnotes provided on last page of table.

Table 4. Key Baseline Characteristics (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

	Sotorasib (N = 171)	Docetaxel (N = 174)	Total (N = 345)
Best response on prior therapy - n (%)			
Primary refractory (progression on first scan)	67 (39.2)	57 (32.8)	124 (35.9)
Suboptimal response (stable disease)	50 (29.2)	53 (30.5)	103 (29.9)
Recurrent (initial response with subsequent growth)	35 (20.5)	47 (27.0)	82 (23.8)
Not evaluable	10 (5.8)	11 (6.3)	21 (6.1)
Non-PD/Non-CR	9 (5.3)	6 (3.4)	15 (4.3)
Time from Initial diagnosis to randomization (month)			
n	162	161	323
Mean	23.33	24.47	23.90
SD	21.28	27.56	24.58
Median	16.21	16.92	16.69
Min, Max	2.3, 132.3	1.5, 227.3	1.5, 227.3
PD-L1 protein expression (%) - n (%)			
< 1	57 (33.3)	55 (31.6)	112 (32.5)
≥ 1 to < 50	46 (26.9)	70 (40.2)	116 (33.6)
≥ 50	60 (35.1)	40 (23.0)	100 (29.0)
Details of specific co-mutation/co-alteration at baseline[d]			
EGFR	1 (0.6)	0 (0.0)	1 (0.3)
BRAF	1 (0.6)	1 (0.6)	2 (0.6)
ALK	1 (0.6)	0 (0.0)	1 (0.3)
MET	1 (0.6)	2 (1.1)	3 (0.9)
ROS1	1 (0.6)	0 (0.0)	1 (0.3)
TP53	4 (2.3)	6 (3.4)	10 (2.9)
STK11	4 (2.3)	4 (2.3)	8 (2.3)
KEAP1	2 (1.2)	1 (0.6)	3 (0.9)

Page 2 of 2

CNS = central nervous system; CR = complete response; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; N = number of patients in the analysis set; n = number of patients with observed data; PD = progressive disease; PFS = progression-free survival

Data cut-off date = 02 August 2022

History of CNS involvement was the presence of brain metastasis at baseline.

[a] Same patient can be counted under multiple categories.

[b] Reported data is from anti-cancer therapies (prior) page of CRF.

[c] Reported data is from anti-cancer therapies (prior) page of CRF and per Amgen Medical Monitor review.

[d] Specific co-mutation data is from mutation detection method page of CRF. HER2, RET, NTRK, NRAS, and PIK3CA comutations were also tested for, but no patient was identified with these comutations so they were not included in the table.

Source: Modified from Table 14-2.1.2 of CodeBreaK 200 Primary Analysis

5.1.5 Progression-free Survival (Primary Endpoint)

A total of 223 events of PFS were reported as of the data cutoff date (02 August 2022), including 122 patients (71.3%) in the sotorasib group and 101 patients (58.0%) in the docetaxel group. The median PFS as assessed by central review was 5.6 months (95% CI: 4.3, 7.8) in the sotorasib group compared with 4.5 months (95% CI: 3.0, 5.7) in the docetaxel group (Table 5 and Figure 5). The HR for PFS following treatment with sotorasib vs docetaxel was 0.663 (95% CI: 0.509, 0.864; p = 0.003), demonstrating a

34% reduction in the risk of progression or death with sotorasib vs docetaxel. The Kaplan-Meier estimated PFS rates were 46.5% and 39.1% at 6 months, and 24.8% and 10.1% at 12 months for sotorasib and docetaxel, respectively.

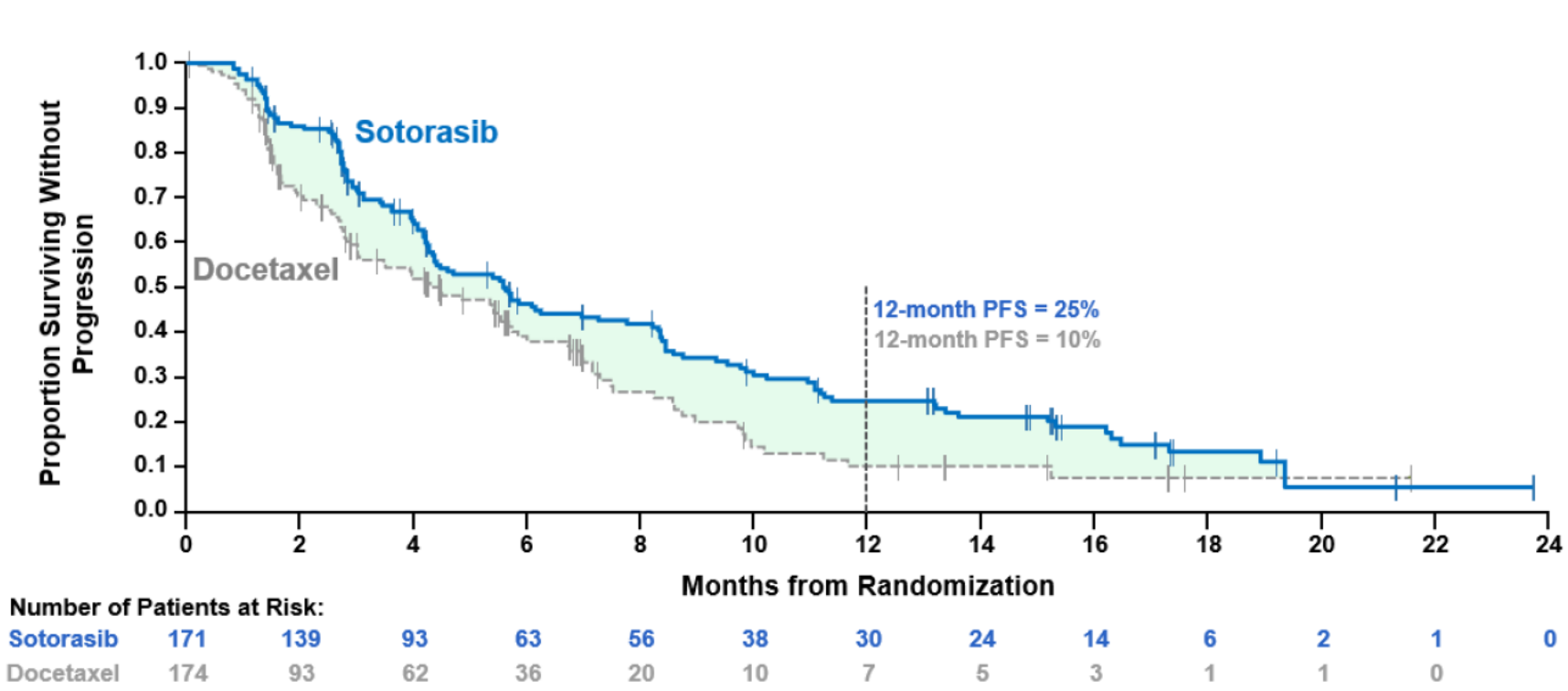
The PFS benefit observed in the sotorasib group vs the docetaxel was consistent across all relevant prespecified subgroups, including history of CNS involvement and liver metastasis at baseline (Figure 6).

Table 5. Summary of Progression-free Survival Results as Assessed by Blinded Independent Central Review (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

	Sotorasib (N = 171)	Docetaxel (N = 174)	Treatment Difference (Sotorasib vs Docetaxel)
Progression-free survival (PFS)			
PFS events – n (%)	122 (71.3)	101 (58.0)	
Kaplan-Meier Median (months) (95% CI)	5.62 (4.27, 7.75)	4.47 (3.02, 5.68)	
Hazard ratio (95% CI)			0.663 (0.509, 0.864)
Stratified log-rank p-value			0.003
PFS rate (95% CI) - %			
3 months	71.73 (64.01, 78.08)	59.42 (50.66, 67.13)	
6 months	46.49 (38.27, 54.30)	39.06 (30.22, 47.79)	
12 months	24.84 (17.90, 32.38)	10.12 (4.68, 18.02)	

BICR = blinded independent central review; CNS = central nervous system
Patients who did not have disease progression per BICR assessments and started new anti-cancer therapy including crossover were censored at the last evaluable BICR assessment.
Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards model.
Stratification factors included number of prior lines of therapy in advanced disease (1 vs 2 vs ≥ 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no).
Notes: Data cut-off date = 02 August 2022
Source: Modified from Table 14-4.2.1 and Table 90920230727-4.9.1 of CodeBreaK 200 CodeBreaK 200 Primary Analysis

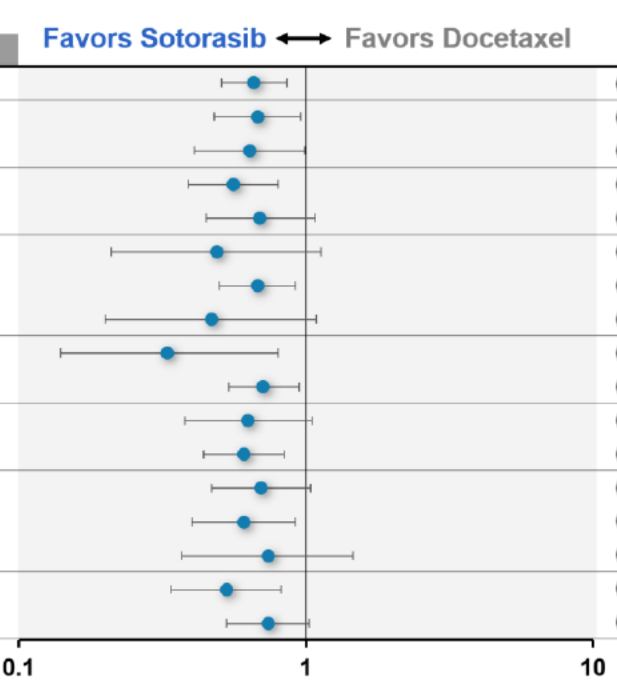
Figure 5. Progression-free Survival Kaplan-Meier Curves as Assessed by the Blinded Independent Central Review Committee (Full Analysis Set) (CodeBreaK 200 Primary Analysis)



Data cut-off date = 02 August 2022
Source: Modified from Figure 14-4.1.1 of CodeBreaK 200 Primary Analysis

Figure 6. Forest Plot of Key Subgroup Analyses of Progression-free Survival as Assessed by the Blinded Independent Central Review Committee (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

Subgroup		Patients, n Sotorasib	Patients, n Docetaxel	HR (95%CI)
All randomized patients		171	174	**0.66** (0.51, 0.86)
Age at baseline, yrs	<65	91	95	**0.68** (0.48, 0.96)
	≥65	80	79	**0.64** (0.41, 0.99)
Sex	Male	109	95	**0.56** (0.39, 0.80)
	Female	62	79	**0.69** (0.45, 1.08)
Region	North America	20	22	**0.49** (0.21, 1.13)
	Europe	126	126	**0.68** (0.50, 0.92)
	Other	25	26	**0.47** (0.20, 1.09)
Race	Asian	21	22	**0.33** (0.14, 0.80)
	Non-Asian	149	151	**0.71** (0.54, 0.95)
Baseline ECOG status	0	59	59	**0.63** (0.38, 1.05)
	1	112	115	**0.61** (0.44, 0.84)
Number of prior lines in advanced disease	1	77	78	**0.70** (0.47, 1.04)
	2	65	69	**0.61** (0.40, 0.92)
	>2	29	27	**0.74** (0.37, 1.46)
History of CNS involvement	Yes	58	60	**0.53** (0.34, 0.82)
	No	113	114	**0.74** (0.53, 1.03)



CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; PFS = progression-free survival
Hazard ratios (sotorasib vs docetaxel) and 95% CIs were estimated using a stratified Cox proportional hazards model.
Data cut-off date = 02 August 2022.
Source: Modified from Figure 14-4.1.5 of CodeBreaK 200 Primary Analysis

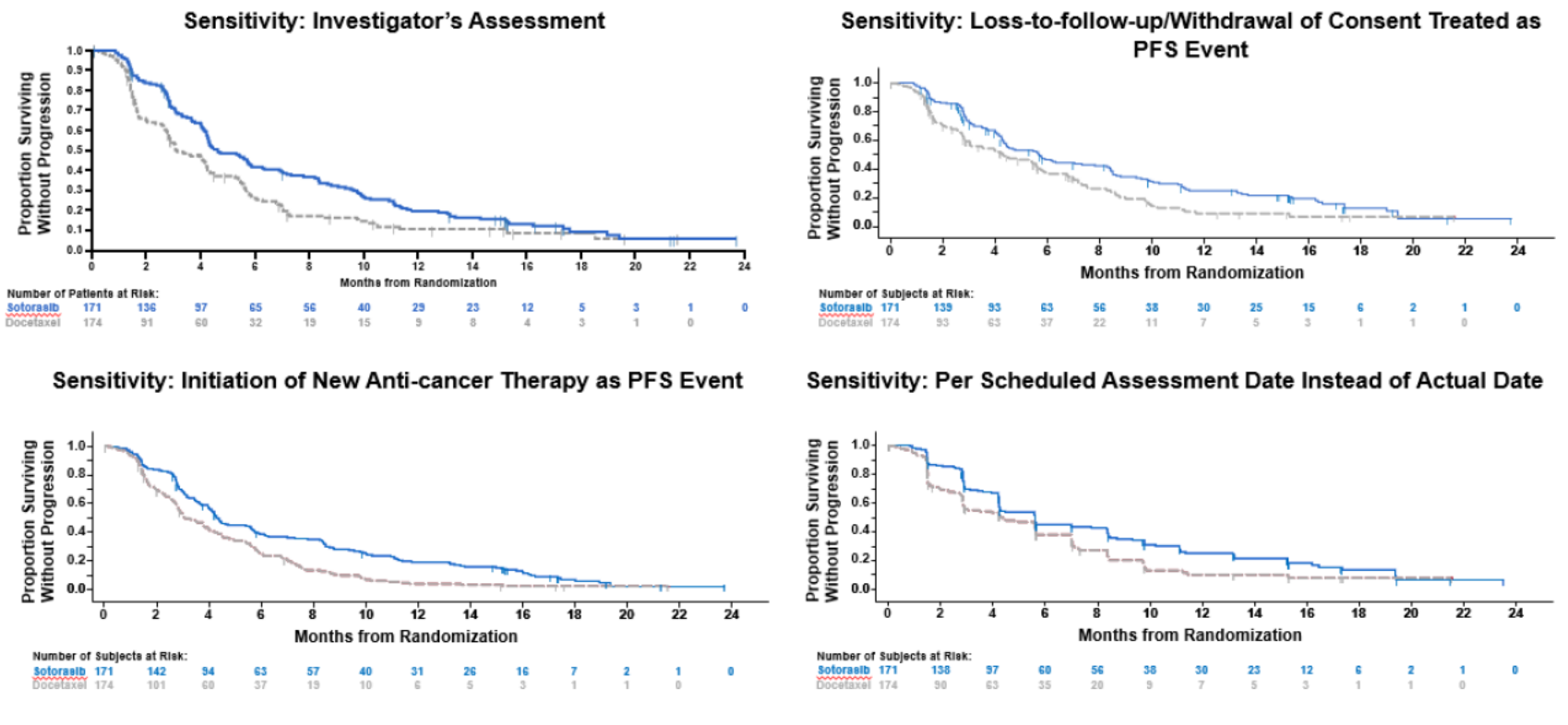
5.1.5.1 Pre-specified Progression-free Survival Sensitivity Analyses

The CodeBreaK 200 SAP prespecified multiple sensitivity analyses including investigator assessment of PFS, unstratified cox regression model, and alternative censoring rules for the primary endpoint of PFS. Results from the unstratified analysis reported HR of 0.692 (95% CI: 0.528, 0.908; descriptive p = 0.007). The alternative censoring rules included considering initiation of new anti-cancer therapy as an event; patients who were lost to follow-up or withdrew consent were treated as having an event at the next scheduled assessment; and using the closest scheduled visit date as progression or censoring date. The Kaplan-Meier curves for each of these sensitivity analyses are provided in Figure 7.

- Sensitivity analysis for initiation of new anti-cancer therapy treated as a PFS event with a HR (95% CI) = 0.60 (0.47, 0.76).
- Sensitivity analysis for lost to follow-up or consent withdrawal treated as having an event at the next scheduled assessment with a HR (95% CI) = 0.65 (0.50, 0.85).
- Sensitivity analysis for using closest scheduled visit date as progression or censoring date with a HR (95% CI) = 0.66 (0.51, 0.86).

Results from all prespecified sensitivity analyses confirmed the robustness of the PFS primary analysis result. Results from the analysis of PFS as assessed by the investigators were also consistent with those per central review (HR = 0.645, 95% CI: 0.504, 0.824; descriptive $p < 0.001$) (Figure 7).

Figure 7. Prespecified PFS Sensitivity Analyses (CodeBreaK 200)



PFS = progression-free survival
Data cutoff date = 02 August 2022
Source: Modified from Figure 14-4.1.2, Figure 90920230628-4.1.6, Figure 90920230628-4.1.4, and Figure 90920230628-4.1.5 of CodeBreaK 200 Primary Analysis

5.1.5.2 Additional Progression-free Survival Analyses

Additional analyses for PFS were explored to address potential sources of bias in the PFS primary analysis dataset. These results (summarized in Table 6) showed that the PFS advantage seen with sotorasib vs docetaxel was consistent across analyses, confirming the robustness of the primary endpoint.

Table 6. Summary of Additional PFS Analyses

Potential Source of Bias	Analysis Method and Section	Results
Potential imbalance of covariates due to early patient withdrawal	Covariate adjusted analysis Section 5.1.11.3.1	HR = 0.60 (0.46, 0.79) Table 15
Differentiated randomized-not-treated and early censoring patients: the 2 treatment groups had different numbers of patients who were randomized and not treated or prematurely discontinued the treatment after a very short period of follow up.	Imputations of patients randomized-not-treated in docetaxel group by resampling to evaluate whether the PFS treatment effect is robust under the impact of differential early withdrawal (resampling from patients who have not progressed or died by 6 weeks) Section 5.1.11.3.2	HR = 0.70 (0.54, 0.90) Table 16
Scan interval: Tumor assessments were performed at time intervals (ie, every 6 weeks until week 49 and then at 9-week intervals thereafter with +/- 1 week window), so the time of disease progression cannot be precisely measured	Interval censoring Section 5.1.11.5	HR = 0.72 (0.55, 0.94) Table 17
A significant HR was reported with moderate difference in median PFS due to Kaplan-Meier curves getting closer at the median time.	Restricted Mean Survival Time was assessed as an alternative measure for treatment benefit Section 5.1.11.6	Average PFS time at 1-year follow-up is increased by 11.1% (95% CI:3.3%, 18.9%) in sotorasib vs docetaxel Table 18

HR = hazard ratio; PFS = progression free survival

5.1.6 Objective Response Rate by Central Review (Key Secondary Endpoint)

Sotorasib demonstrated a statistically significant improvement in ORR over docetaxel. The ORR was tested at 2-sided 0.01 level after the PFS hypothesis was rejected per prespecified statistical testing strategy (Section 5.1.2.1). An objective response was achieved for 48 patients (complete response for 2 patients, partial response for 46 patients) in the sotorasib group, and for 23 patients (all partial response) in the

docetaxel group. The ORR (95% CI) was 28.1% (21.5, 35.4) in the sotorasib group compared with 13.2% (8.6, 19.2) in the docetaxel group (odds ratio of 2.600; 95% CI: 1.483, 4.557; p < 0.001) (Table 7). Results from subgroup analyses for ORR were consistent with those of the primary analysis.

Table 7. Summary of Objective Response Rate Results as Assessed by the Blinded Independent Central Review Committee (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

	Sotorasib (N = 171)	Docetaxel (N = 174)	Treatment Difference (Sotorasib vs Docetaxel)
Best Overall Response			
Complete response (CR)	2 (1.2%)	0 (0.0%)	
Partial response (PR)	46 (26.9%)	23 (13.2%)	
Stable disease	93 (54.4%)	82 (47.1%)	
Objective Response Rate (ORR)			
Responders (PR or CR)	48	23	
ORR (95% CI)[a]	28.1% (21.5%, 35.4%)	13.2% (8.6%, 19.2%)	
ORR difference (95% CI)[a]			14.8% (6.4%, 23.1%)
ORR odds ratio (95% CI)[b]			2.60 (1.48, 4.56)
p-value[b]			< 0.001

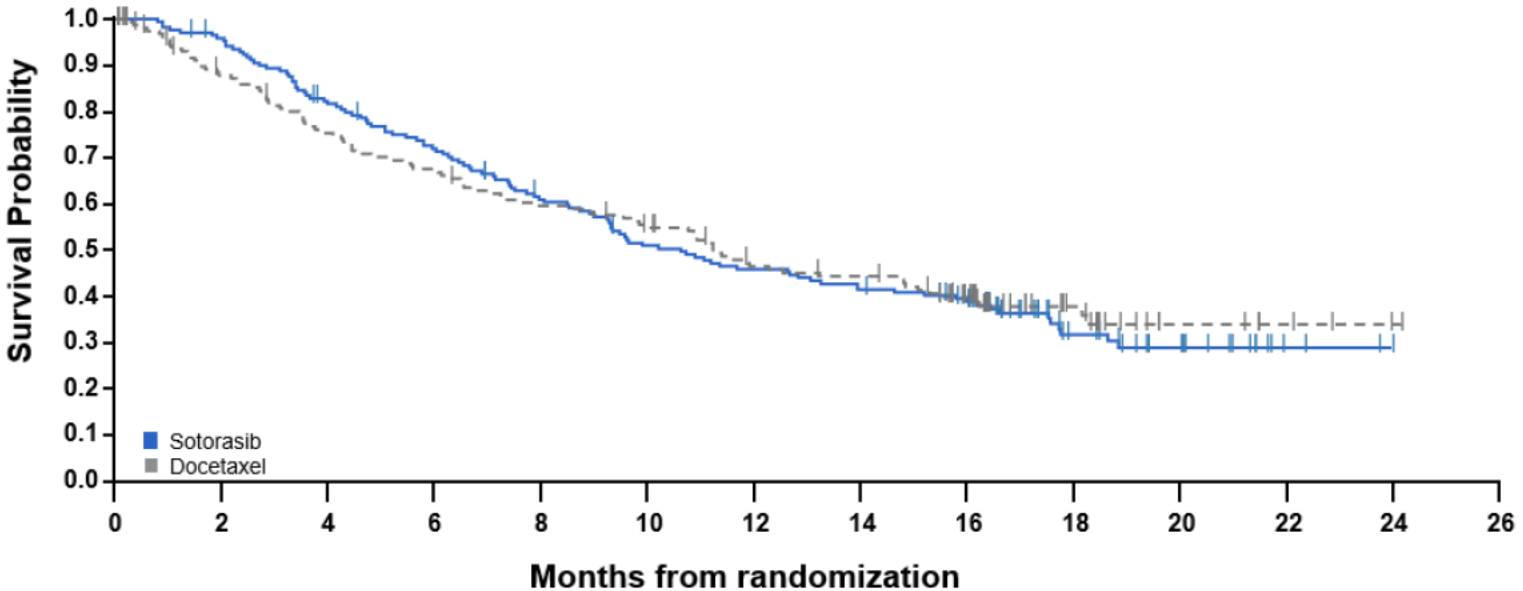
CNS = central nervous system CR = complete response; ORR = overall response rate; PR = partial response
Percentages were based on total number of randomized patients in each treatment group (N).
Randomization stratification factors were number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no).
[a] 95% CIs were estimated using the Clopper-Pearson method.
[b] p-value were estimated using the Cochran Mantel Haenszel chi-square test controlling for the randomization stratification factors.
Data cutoff date = 02 August 2022
Source: Modified from Table 14-4.3.1 of CodeBreaK 200 Primary Analysis

5.1.7 Overall Survival (Key Secondary Endpoint)

At the time of the primary analysis (02 August 2022), 203 deaths were reported, which reached the target number of events for OS primary analysis. The formal testing for OS comparing patients in the sotorasib group with patients in the docetaxel group did not achieve statistical significance (at 2-sided 0.05 significance level given ORR hypothesis was rejected). The median OS was 10.64 months (95% CI: 8.94, 13.96) in the sotorasib group and 11.30 months (95% CI: 9.00, 14.85) in the docetaxel group with stratified Cox HR = 1.010 (95% CI: 0.766, 1.331; stratified log-rank p = 0.94) (Figure 8 and Table 20).

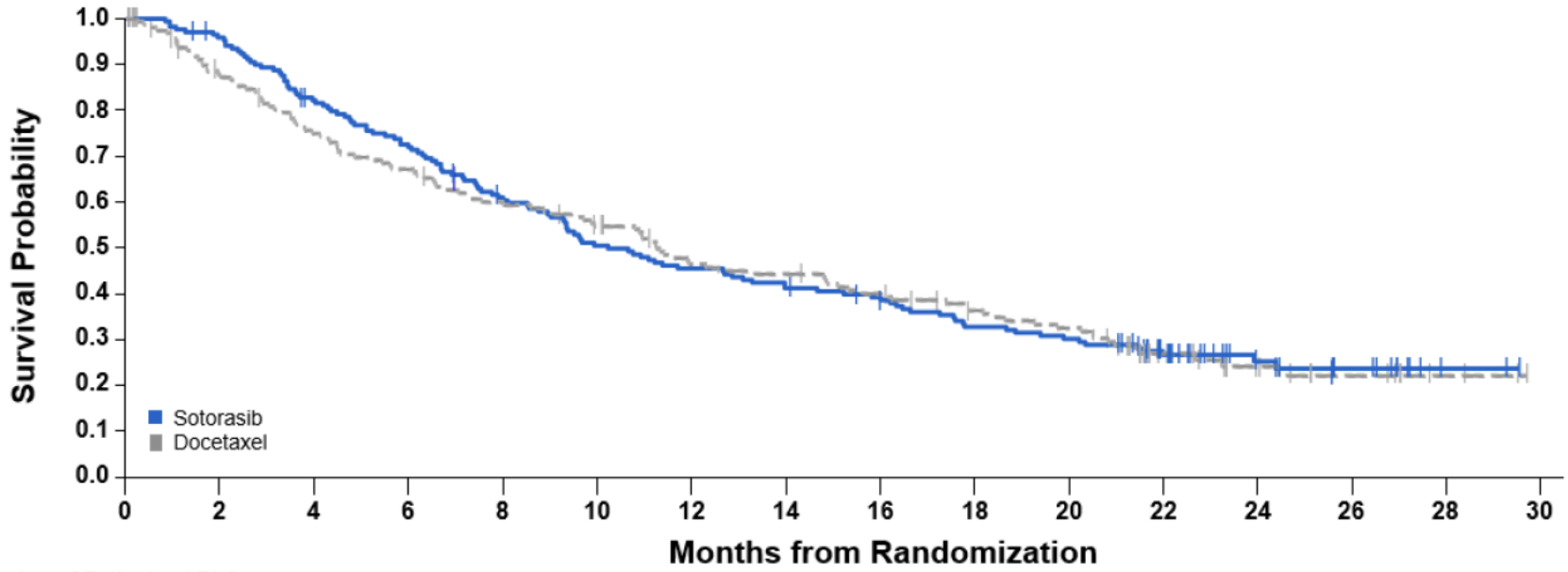
At the time of the 90-day safety update (18 January 2023), the updated OS results showed an HR for sotorasib vs docetaxel of 0.957 (95% CI: 0.741, 1.235). While the median OS only estimates the OS time at a single 50th percentile point of the Kaplan-Meier curve, the HR measures the overall treatment effect in survival throughout the duration of follow-up. The updated OS results with narrow HR 95% CI did not suggest a survival detriment for patients treated with sotorasib (Figure 9 and Table 20). Results from subgroup analyses for OS were consistent with those of the primary analysis (Figure 10). There were 46 patients in the docetaxel group who crossed over to receive sotorasib after centrally-confirmed progressive disease per study design (Section 5.1.11.7). In addition, there were 13 patients who received sotorasib as subsequent therapies outside study treatments.

Figure 8. Overall Survival Kaplan-Meier Curves (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)



OS=overall survival;
PFS = progression-free survival;
Censor indicated by vertical bar |.
Data cut-off date = 02 August 2022
Source: Modified from Figure 14-4.3.1 of CodeBreaK 200 Primary Analysis

**Figure 9. Overall Survival Kaplan-Meier Curves (Full Analysis Set)
(CodeBreaK 200 90-Day Safety Update Ad-hoc Analysis – 18 January 2023 Data Cutoff)**



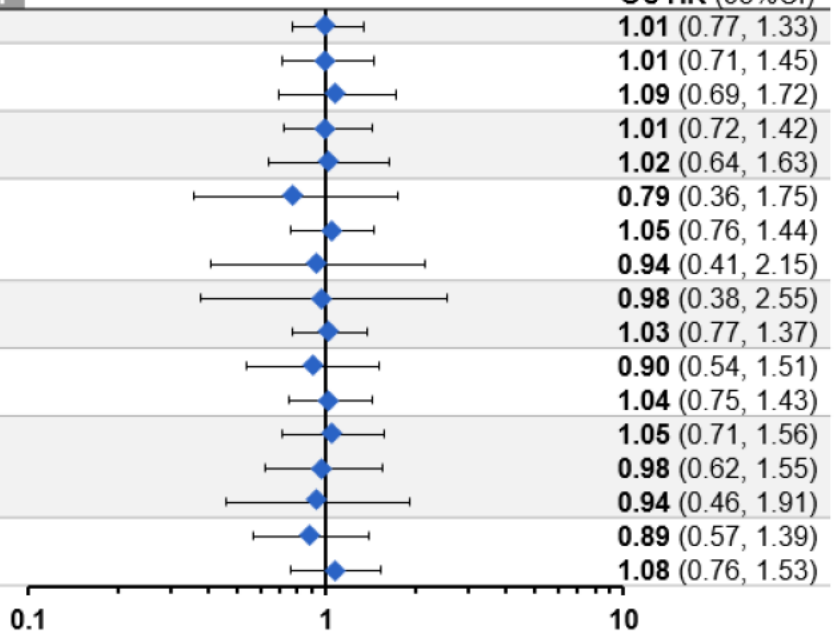
Number of Patients at Risk:

Sotorasib	171	162	137	120	98	82	74	67	62	51	47	32	17	11	2	0
Docetaxel	174	136	116	104	91	82	67	64	57	48	43	23	13	8	3	0

HR = hazard ratio; OS = overall survival
Censor indicated by vertical bar
Survival curves and median OS derived by Kaplan-Meier method, while HR (95% CI) reported from Cox proportional hazards model and p-value was calculated using log-rank test stratified by randomization stratification factors
HR < 1.0 indicated lower average death rate and longer OS for sotorasib relative to docetaxel
Data cut off date: 18 January 2023
Source: Modified from Figure 14-4.3.1 of CodeBreaK 200 90-day Safety Update

Figure 10. Forest Plot Key Subgroup Analyses of Overall Survival (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

Subgroup		Patients, n Sotorasib	Patients, n Docetaxel	OS HR (95%CI)
All randomized patients		171	174	**1.01** (0.77, 1.33)
Age at baseline, yrs	<65	91	95	**1.01** (0.71, 1.45)
	≥65	80	79	**1.09** (0.69, 1.72)
Sex	Male	109	95	**1.01** (0.72, 1.42)
	Female	62	79	**1.02** (0.64, 1.63)
Region	North America	20	22	**0.79** (0.36, 1.75)
	Europe	126	126	**1.05** (0.76, 1.44)
	Other*	25	26	**0.94** (0.41, 2.15)
Race	Asian	21	22	**0.98** (0.38, 2.55)
	Non-Asian	149	151	**1.03** (0.77, 1.37)
Baseline ECOG status	0	59	59	**0.90** (0.54, 1.51)
	1	112	115	**1.04** (0.75, 1.43)
Number of prior lines in advanced disease	1	77	78	**1.05** (0.71, 1.56)
	2	65	69	**0.98** (0.62, 1.55)
	>2	29	27	**0.94** (0.46, 1.91)
History of CNS involvement	Yes	58	60	**0.89** (0.57, 1.39)
	No	113	114	**1.08** (0.76, 1.53)



CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; OS = overall survival; PFS = progression-free survival

Randomization stratification factors were number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no).

Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards model. A hazard ratio < 1.0 indicated a lower average event rate and a longer PFS for sotorasib relative to docetaxel.

History of CNS involvement was the presence of brain metastasis at baseline.

*Other includes South America, Asia, and Australia

Data cut-off date = 02 August 2022.

Source: Modified from Figure 14-4.3.2 of CodeBreaK 200 Primary Analysis

5.1.7.1 Pre-specified Overall Survival Sensitivity Analysis

The OS sensitivity analyses adjusting for cross over were carried out per the SAP using 3 statistical methods: rank preserving structural failure time (Robins et al, 1991), inverse probability of censoring weighting (Robins et al, 1993), and 2-stage approach (Latimer, 2014). The crossover adjusted OS analyses (Table 8) showed consistent results with the OS primary analysis results.

Table 8. Overall Survival – Sensitivity Analysis Adjusting for Crossover (Full Analysis Set) (CodeBreaK 200 – PFS Primary Analysis)

	Sotorasib (N = 171)	Docetaxel (N = 174)	Treatment Difference
RPSFTM adjusted			
Events/subjects after crossover adjustment (%)	109/171 (63.7)	94/174 (54.0)	
Acceleration Factor (95% CI) [a]			0.989 (0.668, 1.522)
Hazard Ratio (95% CI) [b]			1.010 (0.660, 1.492)
IPCW adjusted			
Events/subjects after crossover adjustment (%)	109/171 (63.7)	77/174 (44.3)	
Hazard Ratio (95% CI) [b]			0.990 (0.733, 1.337)
Two-stage approach adjusted			
Events/subjects after crossover adjustment (%)	109/171 (63.7)	75/174 (43.1)	
Acceleration Factor (95% CI) [c]			1.731 (0.799, 3.749)
Hazard Ratio (95% CI) [b]			0.920 (0.409, 1.300)

The data is merged by the as-is snapshot dated 01SEP2023 for the updated Confirmation Of Progression (COP) data filtered back to the PA DCO of 02AUG2022, and the rest of the ADaM datasets from the PA clean snapshot dated 23AUG2022.
N = Number of patients in the analysis set. RPSFTM = Rank Preserving Structural Failure Time Model. IPCW = Inverse Probability of Censoring Weighting.
Randomization stratification factors are number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no).
[a] A g-estimation procedure is used to find the value of the acceleration factor and its 95% CI such that the counterfactual overall survival times are balanced across the treatment groups. Re-censoring is applied to the counterfactual overall survival times.
[b] Hazard ratios are estimated using a stratified Cox proportional hazard model. 95% CIs are estimated using bootstrapping (1000 samples) for RPSFTM and TSE and robust variance estimation for IPCW.
[c] To estimate the acceleration factor, a Weibull accelerated failure time model is fit to the overall survival data of docetaxel patients from the secondary baseline onwards.
The secondary baseline date is the date of the first PD by investigator subsequently confirmed by independent central confirmation of progression. 57 docetaxel patients are included in the Weibull model fitting based on their available secondary baseline. Of these patients, 45 crossed over to receive sotorasib.
Source: Modified from Table 14-4.1.501 of CodeBreaK 200 Primary Analysis

5.1.7.2 Additional Overall Survival Additional Analysis

More patients prematurely withdrew from the study or were lost to follow-up and censored in the OS primary analysis in the docetaxel group than in the sotorasib group.

Additional covariate adjusted analyses for OS were conducted to address the potential imbalance of covariates due to early discontinuation (Table 9). The result is consistent with the primary analysis result for OS. The analysis showed similar treatment effect to the OS primary analysis.

Table 9. Sensitivity Analysis (CodeBreaK 200): Covariate-adjusted Stratified Cox Model for OS

Stratified Cox Model = Treatment + Covariates	HR (95% CI)	Descriptive p-value
Treatment (sotorasib vs docetaxel)	1.01 (0.76, 1.345)	0.94
Covariates		
Liver metastasis (Y vs N)	1.45 (0.96, 2.19)	0.075
Baseline tumor burden (>mSLD vs <=mSLD)	1.78 (1.30, 2.43)	0.001
ECOG (1 vs 0)	1.72 (1.23, 2.405)	0.002
Age (>=65 vs <65)	0.84 (0.62, 1.13)	0.25
Region (North America vs rest of world)	1.02 (0.67, 1.55)	0.93

ECOG = Eastern Cooperative Oncology Group; mSLD = median of sum of diameters in target lesions (71 mm)

Source: Table 90920230811-4.14.3 of CodeBreaK 200 Primary Analysis

5.1.8 Secondary Endpoints: Duration of Response, Time to Response, and Disease Control Rate

At the time of the primary analysis (02 August 2022) (Table 10), the secondary endpoints of DOR, TTR, and DCR were improved for sotorasib vs docetaxel. A waterfall plot showing best percentage change from baseline in sum of diameters for BICR-assessed best overall response is shown in Figure 11. A swimmer plot of BICR-assessed TTR and DOR for the 48 responders in the sotorasib group and the 23 responders in the docetaxel group is shown in Figure 12.

Table 10. Summary of Duration of Response, Time to Response, and Disease Control Rate Results by BICR – CodeBreaK 200 (Full Analysis Set) (CodeBreaK 200 Primary Analysis)

	Sotorasib (N = 171)	Docetaxel (N = 174)	Treatment Difference
Disease control rate (DCR)			
Number of patients who achieved disease control	141	105	
DCR (95% CI)[a]	82.5 (75.9, 87.8)	60.3 (52.7, 67.7)	
Odds ratio (95% CI)[b]			3.077 (1.862, 5.085)
Difference of proportions of disease control (95% CI)[b]			21.8 (12.6, 31.0)
Duration of response (months)[c]			
Number of patients with confirmed BOR of PR or CR	48 (28.1)	23 (13.2)	
Median (95% CI)[d]	8.64 (7.06, 17.97)	6.80 (4.27, 8.28)	
Min, Max (+ for censored)	1.1+, 22.5+	1.4+, 16.3+	
Time to response (months)			
Number of patients with confirmed BOR of PR or CR	48	23	
Median	1.41	2.76	
Min, Max	1.2, 8.3	1.3, 11.3	

BOR = best overall response; CNS = central nervous system; CR = complete response; N = number of patients in the analysis set; n = number of patients with observed data; PR = partial response; TTR = time to response

Months were derived as number of days from randomization date to event/censor date * 12/365.25.

Randomization stratification factors were number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no).

[a] 95% CIs were estimated using the Clopper-Pearson method.

[b] Odds ratio/ Difference of proportions, its 95% CIs and p-values are calculated using the stratified Cochran-Mantel-Haenszel Chi-square test.

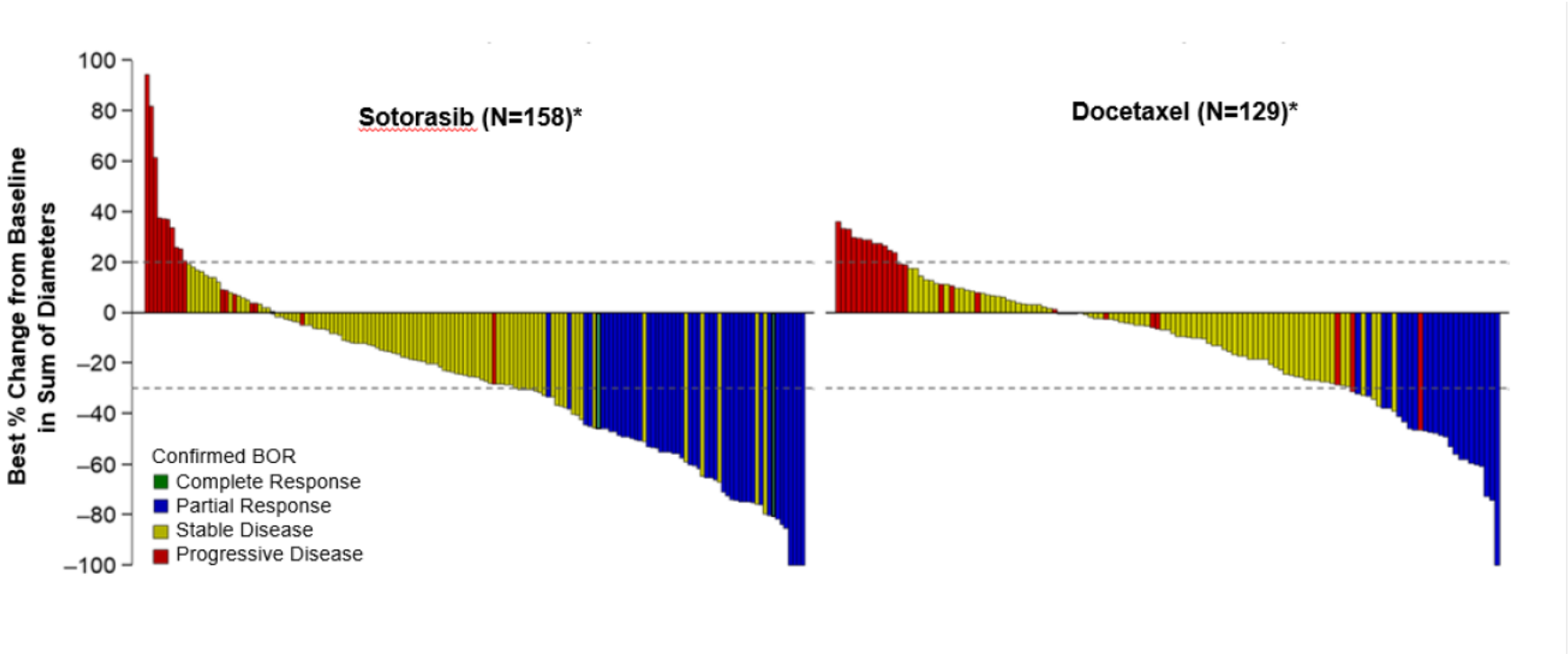
[c] DOR and TTR were calculated only for patients who achieve a confirmed best overall response of PR or CR.

[d] Medians, percentiles and 95% CIs are estimated using the Kaplan-Meier method.

Data cutoff date = 02 August 2022.

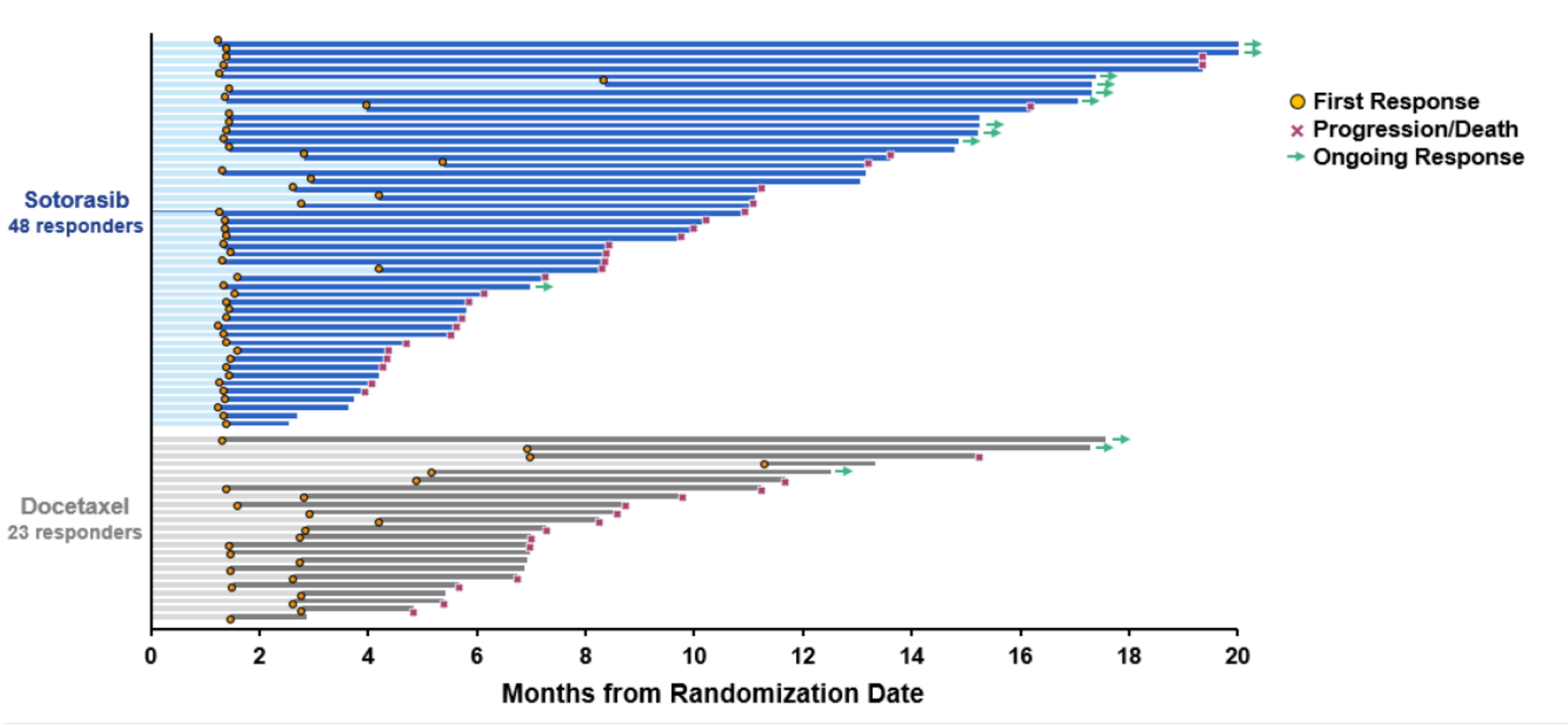
Source: Modified from Table 14-4.3.1 of CodeBreaK 200 Primary Analysis

Figure 11. Waterfall Plot for Percentage Change From Baseline in Sum of Diameters for Best Overall Response Assessed by the Blinded Independent Central Review Committee (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)



BOR = best overall response; PFS = progression-free survival; NE = not estimable
This plot presents the deepest response per patient by the largest percent reduction, if applicable, in sum of diameters from baseline up to the tumor assessment when the first progressive disease occured or before the start of the new anti-cancer therapy including crossover, whichever was earlier.
*Patients without baseline target lesions or post-baseline percent changes, or with BOR of NE are not shown.
Median of best percent change from baseline in sum of target lesions in confirmed responders was -58.8% for sotorasib group and -48.7% for docetaxel group.
Percent of patients with tumor shrinkage (patients with negative percent change from baseline) was 80.4% for sotorasib group and 62.8% for docetaxel group.
Data cutoff date: 02 August 2022
Source: Modified from Figure 14-4.1.501 of CodeBreaK 200 Primary Analysis

Figure 12. Swimmer Plot of Time to Response and Duration of Response by the Blinded Independent Central Review Committee (CodeBreaK 200 PFS Primary Analysis)



PFS = progression-free survival
Data cutoff date: 02 August 2022
Source: Modified from Figure 14-4.1.503 of CodeBreaK 200 Primary Analysis

5.1.9 Patient-reported Outcomes (Key Secondary Endpoints, Secondary Endpoints, and Ad Hoc Analyses)

Patient-reported outcomes (any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else) may provide direct evidence of treatment benefit on how patients feel or function. In CodeBreaK 200, PROs were collected at the beginning of each treatment cycle (prior to docetaxel administration, mostly referring to the past 7 days or to the time of data collection), and additionally for EuroQol-5 dimension on day 5 of cycle 1, 2, and 3). The PROs were assessed by multiple instruments, including: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and its lung cancer-specific module European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 13 (EORTC QLQ-LC13), the EuroQol-5 Dimension 5 Level (EQ-5D-5L) including the visual analog scale (VAS), the single item GP5 of the Functional Assessment of Cancer Therapy Tool – General Form (FACT-G), and selected items of the PRO - Common Terminology Criteria for Adverse Events (PRO-CTCAE) and, for contextualization, the Brief Pain Inventory (BPI), the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC).

In CodeBreaK 200, the PRO measures were assessed as either key secondary endpoint (change from baseline to week 12 of symptoms: dyspnea [QLQ-C30/LC13 composite], cough [QLQ-LC13], chest-pain [QLQ-LC13], and health-related QoL: physical functioning [QLQ-C30], global health status/QOL [QLQ-C30] or as secondary endpoints [remaining subscales of QLQ-LC13, and the remaining functional scales and dyspnea and fatigue symptom scales of QLQ-C30], time to deterioration of the key secondary endpoints, changes from baseline of VAS as measured by EQ-5D-5L).

Completion rates for QLQ-C30 and QLQ-LC13 among patients in the sotorasib group were high at baseline (98.2% and 97.1% for sotorasib and docetaxel, respectively). As some patients did not initiate docetaxel treatment, the completion rates were lower in the docetaxel group (90.8% and 88.5% for sotorasib and docetaxel, respectively). However, corresponding compliance rates were high (97.6%-98.8% for sotorasib and 96.9%-99.4% for docetaxel at baseline) and remained high (95.9% and 95.5% at week 12 for sotorasib and docetaxel, respectively). The PROs were only assessed while patients

were on treatment so completion rates of QLQ-C30 and QLQ-LC13 decreased over time, and were 62.0% for sotorasib and 39.7% for docetaxel by week 12.

Using PRO instruments QLQ-C30, QLQ-LC13 and PRO-CTCAE the following symptom domains were covered:

- QLQ-C30: fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties
- QLQ-LC13: dyspnea, cough, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, chest pain, pain in arm, or shoulder, pain in other parts
- PRO-CTCAE: pain, aching muscles, aching joints, mouth or throat sores, numbness, mouth cracking, itchy skin

Exploratory and ad hoc analyses of these symptoms using methods consistent with the key secondary endpoints, are described in Section 6.1.12. Results from the safety-related PRO of how bothered patients were by their side effects are summarized in Section 6.1.12.

As the OS was not statistically significant and the PRO endpoints can only be formally tested after rejection of the OS hypothesis per the prespecified statistical testing strategy (Section 5.1.2.1), all PRO results are therefore presented as descriptive.

Thresholds to determine clinically meaningful deterioration or clinically meaningful change in the specified PRO endpoints (Table 33 in Appendix 4) were evaluated based on a pooled analysis on a subgroup of patients enrolled in CodeBreaK 200 with treatment assignments masked, and prior to the study primary analysis. The thresholds were constructed as minimally important change within-individual and within-group change, as well as minimally important difference between treatment groups. The analysis to determine minimally important change and minimally important difference was conducted by an independent external analytic group. When the thresholds for clinical meaningfulness were estimated, a high degree of stochastic and methodological uncertainty was observed. Therefore, cumulative distribution functions (CDF), an alternative established method to determine clinical meaningfulness were prespecified (McLeod et al, 2011). Based on this method, clear separation of CDF curves indicated clinical meaningfulness.

5.1.9.1 Dyspnea, Cough, Chest Pain, Global Health Status/Quality of Life and Physical Functioning

Change From Baseline to Week 12: Mixed Model for Repeated Measurements Analyses

The PRO data was collected and showed that change from baseline to week 12 in global health status, physical functioning, and dyspnea favored sotorasib. In the docetaxel group these outcomes worsened over time (change of -6.90, -8.68 and 9.52 points, respectively). In contrast, these outcomes were stabilized in the sotorasib group (change of 0.03, 0.10 and -0.57 points, respectively) (Figure 13; for dypsnea, a lower score indicates improvements, whereas for global health status and physical functioning, a higher score indicates improvements; ie, the results favor sotorasib in all 3 categories).

Change From Baseline to week 12: Generalized Estimating Equation Analyses

From baseline to week 12, patients in the sotorasib group reported an improvement in cough compared with patients in the docetaxel group (odds ratio for better categories = 3.2, 95% CI: 1.5, 6.65), and a positive trend in favor of sotorasib was observed for chest pain (Figure 13).

Clinical Meaningfulness of Change in Baseline to week 12 Analyses

The predefined threshold of clinical meaningfulness was exceeded for physical functioning (8.8 vs 7). For global health status (6.9 vs 7) and dyspnea (10.1 vs 11), the observed differences were slightly below the predefined thresholds. In terms of CDF, at week 12 for global health status, physical functioning dyspnea and cough there was a clear separation between treatment groups, indicating clinical meaningfulness (Figure 23 in Appendix 4). For chest pain, a separation was not observed.

Time to Deterioration Analyses

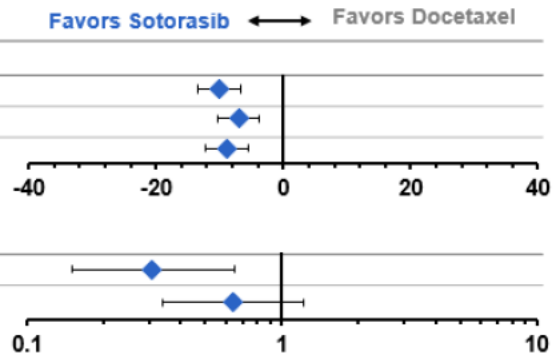
Patients receiving sotorasib maintained better global health status and physical functioning, and showed better scores over time on dyspnea, cough, and chest pain symptoms compared with patients receiving docetaxel. This was assessed by time-to-deterioration analyses defined on the basis of clinically meaningful within-patient change. All of the HRs for the above categories except chest pain had CIs (unadjusted for multiplicity) below 1, meaning that patients felt better longer with sotorasib compared with docetaxel. The results are summarized below and are also shown as part of a benefit:risk Forest plot in Figure 19.

- global health status/QoL: median time-to-deterioration 6.6 weeks docetaxel vs 9.3 weeks sotorasib; HR = 0.694, 95% CI: 0.530, 0.909
- physical functioning: median time-to-deterioration 9.4 weeks docetaxel vs 15.1 weeks sotorasib; HR = 0.692, 95% CI: 0.521, 0.920
- cancer-related symptoms: dyspnea median time-to-deterioration 6.6 weeks docetaxel vs 12.1 weeks sotorasib; HR = 0.629, 95% CI: 0.479, 0.825

- cough: median time-to-deterioration 15.2 docetaxel vs 49.3 weeks sotorasib; HR = 0.553, 95% CI: 0.381, 0.803
- chest pain: median time-to-deterioration 27.3 weeks docetaxel vs 34.9 weeks sotorasib; HR = 0.84, 95% CI: 0.59, 1.18

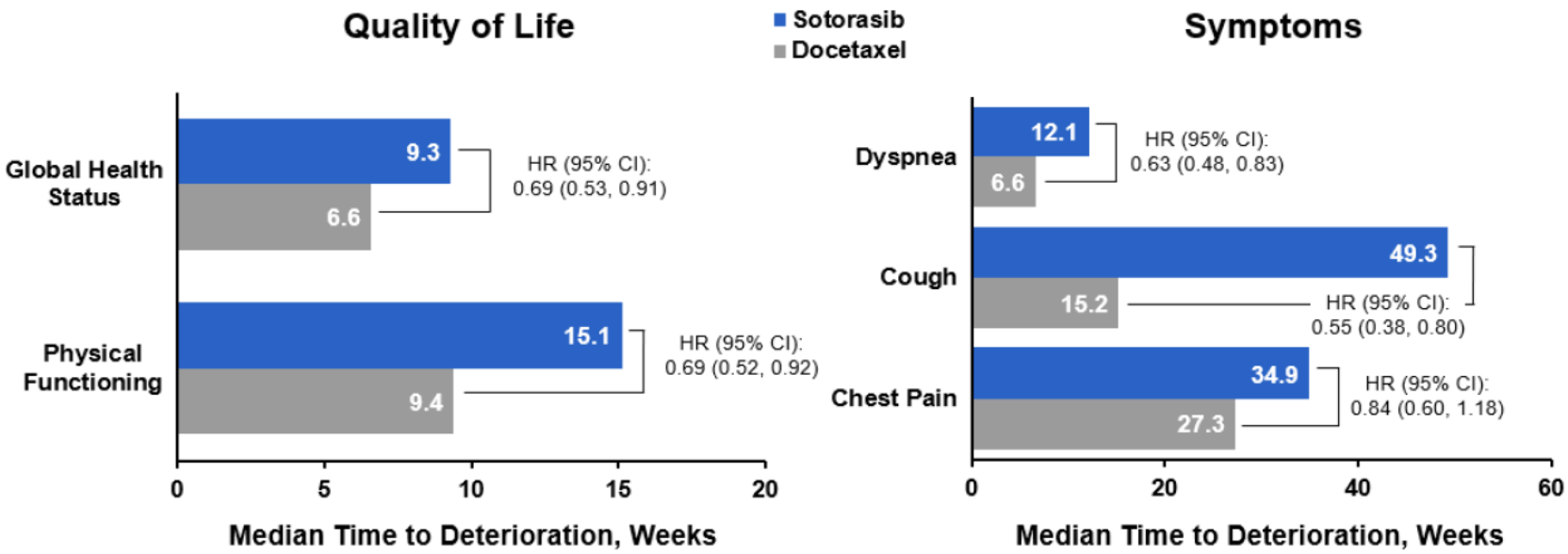
Figure 13. Change in Least Squares Means and Forest Plot of Estimates From Baseline to Week 12 in Global Health Status, Physical Functioning, Dyspnoea, Cough, and Chest Pain (CodeBreaK 200 PFS Primary Analysis)

	Change at week 12		
Key secondary PRO	**Sotorasib**	**Docetaxel**	**Treatment Difference[a]** (95% CI)
Dyspnea (lower score is better)	-0.57	9.52	-10.1 (-13.4, -6.8)
GHS/QOL (higher is better)	0.03	-6.90	-6.9 (-10.2, -3.7)
Physical functioning (higher is better)	0.10	-8.68	-8.8 (-12.2, -5.4)
			Odds ratio[a] (95% CI)
Cough	NR	NR	0.31 (0.15, 0.65)
Chest pain	NR	NR	0.64 (0.34, 1.22)



Number of patients (docetaxel/sotorasib) in MMRMs/GEEs: Dyspnea, cough, chest pain: 122/157 overall and 67/105 at week 12. GHS/QOL and physical functioning: 128/159 overall and 69/106 at week 12.
GHS = NR = Not reported; QOL = quality of life; PFS = progression-free survival; PRO = patient-reported outcome.
Cough and chest pain were assessed as ordinal categorical variable, not continuous score change.
[a] Differences for GHS/QOL and physical functioning were reversed and odds ratios for cough and chest pain were inverted for consistent interpretation of forest plot direction (small value to the left favors sotorasib, large value to the right favor docetaxel). Odd ratio < 1 indicated lower odds of worst cough/chest pain outcome category for sotorasib vs docetaxel.
Data cutoff date: 02 August 2022
Source: Modified from Figure 90920230619-04.2.1 of CodeBreaK 200 Primary Analysis

Figure 14. Patient-reported Outcomes: Time to Deterioration for QLQ-C30 and QLQ-LC13 Scales (EORTC QLQ-C30 and EORTC QLQ-LC13 Analysis Sets) (CodeBreaK 200 PFS Primary Analysis)



Number of patients for docetaxel/sotorasib: GHS/QOL: 130/158; Physical functioning: 129/158; Dyspnea composite score: 123/155; Cough: 114/150; Chest pain: 123/154
EORTC QLQ-LC13 = European Organization for Research and Treatment of Cancer quality of life questionnaire Lung Cancer 13; HR = hazard ratio; PFS = progression-free survival; QLQ-C30 = quality of life questionnaire 30-item core module; QLQ-LC13 = quality of life questionnaire lung cancer module
Data cutoff date: 02 August 2022
Source: Modified from Table 14-11.1.500 and Table 14-11.1.501 CodeBreaK 200 Primary Analysis

5.1.9.2 Changes from baseline of Visual Analog Scale

For QoL as measured by the VAS of the EQ-5D-5L questionnaire for the sotorasib group, no relevant changes from baseline were observed (change of 1.5 points 5 days after administration, and 2.2 points at week 12). In contrast, for the docetaxel group there was immediate worsening (8.4 points 5 days after administration). For the docetaxel group the VAS score also worsened long-term (eg, by 5.8 points at week 12 just prior to administration of sotorasib or docetaxel) (Figure 23 in Appendix 4).

5.1.10 Exploratory Efficacy Endpoints

Progression-free survival 2 and time to progression of CNS disease were prespecified as exploratory endpoints. Progression-free survival 2 was defined as time from the date of randomization to second disease progression or disease progression on next-line treatment (including crossover from docetaxel to sotorasib and start of treatment beyond progression), or death from any cause, whichever occurred first. An event of PFS2 was reported for 121 patients (70.8%) in the sotorasib group and 113 patients (64.9%) in the docetaxel group. Median PFS2 in the sotorasib group was 9.6 months (95% CI: 8.1, 11.1) compared with 7.6 months (95% CI: 6.5, 9.9) in the docetaxel group (HR = 0.867, 95% CI: 0.670, 1.121). The Kaplan-Meier estimate for PFS2 at 6 months was 68.4% and 38.1% at 12 months in the sotorasib group vs 62.3% and 31.5%, respectively, in the docetaxel group (Table 11 and Figure 15).

Table 11. Summary of Progression-free Survival 2 Results (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

	Sotorasib (N = 171)	Docetaxel (N = 174)	Treatment Difference
PFS2			
PFS2 Events – n (%)	121 (70.8)	113 (64.9)	
Hazard ratio (95% CI)[a]			0.867 (0.670, 1.121)

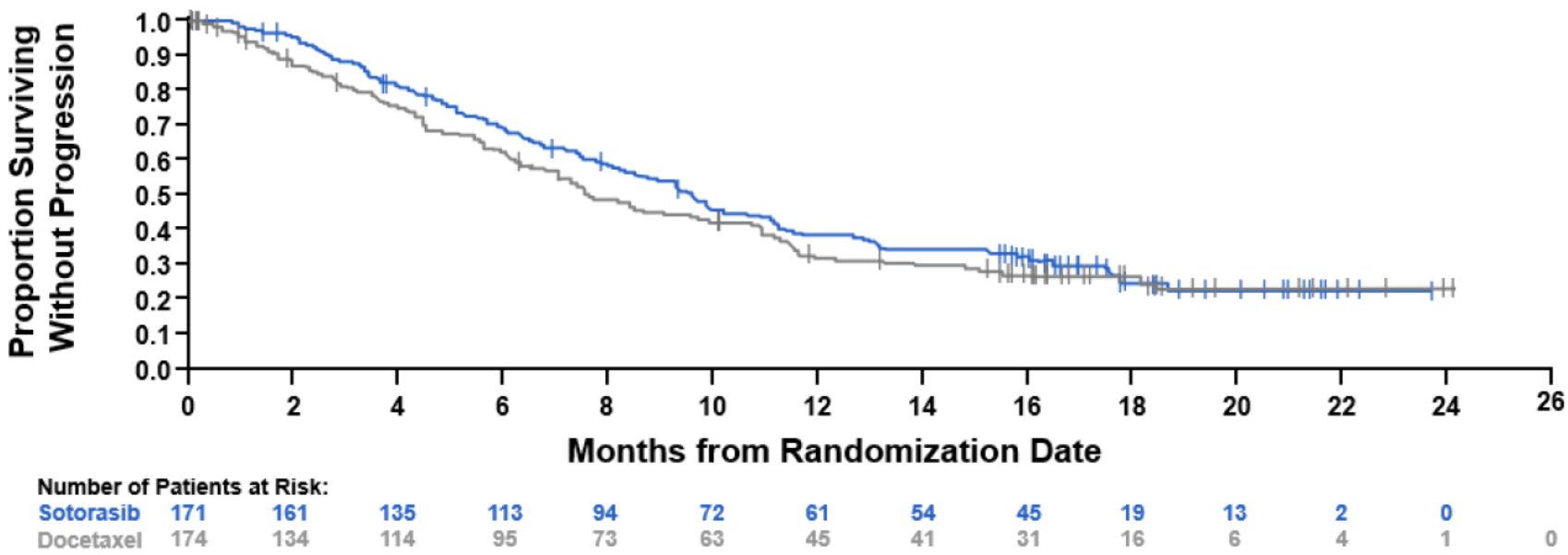
CNS = central nervous system; N = number of patients in the analysis set; n = number of patients with observed data; PFS2 = progression-free survival after second disease progression/disease progression after next line of treatment. The next line of treatment includes patients started post-baseline anti-cancer therapy, crossover from docetaxel to sotorasib and treatment beyond progression.

Randomization stratification factors were number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no).

[a] Hazard ratio and 95% CI are estimated using a stratified Cox proportional hazards model. Randomization stratification factors are number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of CNS involvement (yes vs no). Data cutoff date = 02 August 2022.

Source: modified from Table 14-4.6.1 and Table 14-4.7.1 of CodeBreaK 200 Primary Analysis

Figure 15. Progression-Free Survival 2 Kaplan-Meier Curves (Full Analysis Set) (CodeBreaK 200 PFS Primary Analysis)



PFS = progression-free survival
Data cutoff date: 02 Aug 2022
Censor indicated by vertical bar I.
-PFS2 in this plot is based on primaary analysis PFS2 output.
-Hazard ratios and 95% CIs are estimated using Cox proportional hazard model. A hazard ratio < 1.0 indicates a lower average event rate and a longer PFS2 for sotorasib relative to Docetaxel. P-value is calculated using a stratified log-rank test. "
Source: Modified from Figure 90920230728-4.1.18 of CodeBreaK 200 Primary Analysis

A total of 58 patients (33.9%) in the sotorasib group and 60 patients (34.5%) in the docetaxel group had a history of CNS involvement prior to enrollment. A prespecified subgroup analysis showed that the PFS benefit of sotorasib vs docetaxel was consistent in patients with or without history of CNS involvement (Figure 6). The time to progression of CNS disease was assessed per RECIST criteria among those patients with a history of CNS disease. Of the patients with a history of CNS involvement prior to enrollment, 16 patients in the sotorasib group and 15 patients in the docetaxel group had events of CNS disease progression as determined by investigator assessment. Median time to CNS progression was 15.8 months (95% CI: 9.7, not estimable) in the sotorasib group and 10.5 months (95% CI: 5.8, not estimable) in the docetaxel group (HR = 0.52, 95% CI: 0.26, 1.04) (Table 12).

Table 12. Time to Progression of Central Nervous System Disease (CodeBreaK 200 PFS Primary Analysis)

	Sotorasib (N = 171)	Docetaxel (N = 174)	Treatment Difference
Patients with prior CNS disease	58(33.9)	60 (34.5)	
Patients had recurrent CNS disease - n (%)	16 (27.6)	15 (25.0)	
Time to progression of CNS disease (months)[a]			
Kaplan-Meier Median (95% CI)	15.77 (9.72, NE)	10.48 (5.82, NE)	
Min, Max (+ for censored)	0.0+, 19.4	0.0, 16.2+	
Hazard ratio (95% CI)[b]			0.520 (0.260, 1.038)

CNS = central nervous system; N = number of randomized patients in the study; NE = not estimable; PFS = progression-free survival
[a] Time to progression of CNS disease is calculated for patients with prior CNS disease.
[b] Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards model.
A hazard ratio < 1.0 indicates a lower average event rate and a longer time to event for sotorasib relative to Docetaxel Stratification factors were number of prior lines of therapy in advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian).
Data cutoff date = 02 August 2022.
Source: Modified from Table 14-4.7.1 of CodeBreaK 200 Primary Analysis

Due to the association of metastatic CNS disease with poor prognosis and a negative impact on QoL, a post-hoc analysis of time to progression of CNS disease per BICR review using RANO-BM criteria among patients who had stable/treated CNS lesions was carried out. This demonstrated improved CNS PFS and response and delayed time to progression of CNS disease with sotorasib vs docetaxel: median time to progression of CNS disease was 11.6 months for patients in the sotorasib group vs 6.0 months for patients in the docetaxel group (HR = 0.63, 95% CI: 0.25, 1.62) (Table 13). The median time to progression of CNS disease or all-cause death was 9.6 months vs 4.5 months (HR = 0.53, 95% CI: 0.28, 1.03) for patients in the sotorasib and docetaxel groups

respectively (Table 14). An exploratory analysis showed that the ORR in patients with CNS lesions ≥ 10 mm as measured by BICR was 33.3% in patients in the sotorasib group compared with 15.4% for patients in the docetaxel group. The concordance of systemic and intracranial disease control was higher in patients in the sotorasib group vs patients in the docetaxel group (88% vs 54%, respectively) (Dingemans et al, 2023).

Table 13. Analysis of Time to Central Nervous System Progression Reported by BICR per RANO-BM (Patients with Stable/Treated CNS Lesions at Baseline) (CodeBreaK 200 PFS Primary Analysis)

	Sotorasib (N = 40)	Docetaxel (N = 29)	Treatment Difference
Patients had CNS progression - n (%)	15 (37.5)	10 (34.5)	
Time to CNS progression (months)[a]			
Median (95% CI)	11.60 (5.59, NE)	6.01 (3.35, NE)	
Min, Max (+ for censored)	0.0+, 20.1+	0.0+, 15.5+	
Hazard ratio (95% CI)[b]			0.629 (0.245, 1.615)

BICR = Bblinded independent central review; CNS = central nervous system; N = Number of patients in the analysis set; n = Number of patients with observed data; NE = not estimable; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases

[a] Medians were estimated using the Kaplan-Meier method. 95% CIs were estimated using the method by Klein and Moeschberger with log-log transformation.

[b] Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards model. A hazard ratio < 1.0 indicated a lower average event rate and a longer time to event for sotorasib relative to docetaxel.

Data cut-off date: 02 August 2022

Source: Modified from Table 14-4.4.2 CodeBreaK 200 Primary Analysis

Table 14. Analysis of Time to Progression of Central Nervous System Disease or All-Cause Death (CNS PFS) Reported by BICR per RANO-BM (Patients with Stable/Treated CNS Lesions at Baseline) (CodeBreaK 200 PFS Primary Analysis)

	Sotorasib (N = 40)	Docetaxel (N = 29)	Treatment Difference
Patients had CNS PFS Events - n (%)	21 (52.5)	16 (55.2)	
CNS progressive disease	15 (37.5)	10 (34.5)	
Death	6 (15.0)	6 (20.7)	
CNS PFS (months)[a]			
Median (95% CI)	9.63 (5.09, 17.31)	4.53 (3.09, 7.29)	
Min, Max (+ for censored)	0.0+, 20.1+	0.0+, 15.5+	
Hazard ratio (95% CI)[b]			0.532 (0.275, 1.028)

BICR = blinded independent central review; CNS = central nervous system; N = Number of patients in the analysis set; n = Number of patients with observed data; PFS = progression-free survival; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases

[a] Medianswere estimated using the Kaplan-Meier method. 95% CIs were estimated using the method by Klein and Moeschberger with log-log transformation.

[b] Hazard ratios and 95% CIs were estimated using a stratified Cox proportional hazards model. A hazard ratio < 1.0 indicated a lower average event rate and a longer time to event for sotorasib relative to docetaxel.
Data cut-off date: 02 August 2022
Source: Modified from Table 14-4.1.2 CodeBreaK 200 Primary Analysis

5.1.11 Investigation of Potential Sources of Bias

In order to investigate the robustness of the clinical benefit demonstrated in CodeBreaK 200 and to assess the possible effect of study design and conduct on the results observed, several potential sources of bias were considered. These were either related to study design or study conduct, as discussed in detail in the sections that follow. Study design considerations included the open-label nature of the study, allowance for treatment beyond progression, and crossover from docetaxel to sotorasib. Study conduct considerations included differentiated incidence of patients who were randomized but not treated between treatment groups, informative censoring due to premature anticancer therapy switch by investigators, and discrepancy between the confirmation of progression (COP)-based and BICR-based progression events identified by the imaging vendor while the study was ongoing.

CodeBreaK 200 was rigorously conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. The study was conducted at 148 centers in Europe, North America, Asia, Australia, and South America. Amgen organized investigator and clinical research associate meetings before study start and during the study to provide information on the investigational product, the study rationale and design, and responsibilities under ICH/FDA GCP, and training on the detailed study requirements. The study centers were monitored by Amgen staff and partners, and site visits occurred at regular intervals. Monitors were responsible for reviewing adherence to the protocol, compliance with GCP, and the completeness, accuracy, and consistency of the data. An independent DMC reviewed safety of the study at prespecified timepoints and reviewed the totality of data at the interim analysis. An independent adjudication committee performed blinded reviews of radiology scans and operated in accordance with an imaging charter. In addition, Amgen conducted an audit of this study as part of the independent Amgen Quality, Compliance and Audit program to evaluate compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Consideration of study design and conduct showed that the fundamentals of the study were strong. The clinical benefit demonstrated by the primary analysis of PFS is robust. The efficacy results reported here are able to withstand multiple different sensitivity analyses. Pre-specified sensitivity analyses with alternative censoring rules and PFS per investigator assessments showed consistent results with the primary analysis (Section 5.1.5.1). Additional sensitivity analyses summarized below address several observations in the PFS primary analysis, including scan intervals, differentiated incidence of patients who were randomized but not treated, and potential effects of early censoring. All analyses conducted showed that potential sources of bias did not change the observed treatment effect of sotorasib for the primary endpoint.

5.1.11.1 Study Design and Measures to Mitigate Against Potential Bias

Due to the different methods of administration of sotorasib (daily oral administration) and docetaxel (IV infusion every 3 weeks) and the high disease burden of the patient population who were to be enrolled, an open-label study design was selected. To minimize potential bias, patients were randomized in a 1:1 allocation ratio with randomization accomplished by interactive response technology. In addition, blinded endpoint assessment was used to reduce potential bias resulting from the open-label nature of the study; therefore the primary analysis was based on the objective endpoint of BICR-assessed PFS.

Per protocol amendment 2 (29 June 2020), patients in both the sotorasib and docetaxel groups were allowed to continue treatment beyond progression. Per protocol, treatment beyond progression required that several criteria were met, including no significant or irreversible toxicities related to study treatment, no deterioration in function score, and approval for continuation from the sponsor's medical monitor.

Per protocol Amendment 3 (5 February 2021), the sample size was decreased, an interim analysis was included, and patients in the docetaxel group were permitted to crossover to sotorasib treatment upon centrally confirmed disease progression. Upon centrally confirmed progressive disease, patients could continue on their assigned treatment post-progression (either sotorasib or docetaxel) or patients in the docetaxel group could crossover to sotorasib. Introduction of an option for crossover was anticipated to mitigate against early patient withdrawals from the docetaxel group.

Amendment 3 also established a central COP review. The purpose of the independent central COP was to provide the site investigator with a second, independent opinion

regarding whether the patient had reached progressive disease according to RECIST 1.1 criteria. This measure was implemented to mitigate against the risk that patients would be switched to other anti-cancer therapy premauturely, which would result in informative censoring of the BICR-assessed PFS endpoint. To ensure the independence of the COP review, the imaging vendor assigned a radiologist who was separate from the BICR group to perform reviews to confirm progression. The COP reader did not have knowledge of the treatment assignments of the patients they reviewed.

The study was conducted in a rigorous and robust manner which ensured that, despite the advanced stage of disease and complexity with dosing regimen, the results could be assessed in a standardized, structured, and unbiased way.

5.1.11.2 BICR Assessment of PFS and Imaging Vendor Procedures

To reduce potential bias resulting from the open-label nature of the study, the primary analysis was based on BICR-assessed PFS.

During the course of the study, the imaging vendor identified a discrepancy between the COP-based and BICR-based progression events. In accordance with the imaging charter, the imaging vendor undertook a review of the discordant cases to identify a root cause for the discordance and to assure the quality of the data. Subsequently, Amgen notified FDA of the issue and the proposed resolution from the imaging vendor to re-read selected scans.

In a meeting held on 05 May 2022, the FDA recommended a global re-read of all scans in the study to assure the quality of the imaging data at the time of the primary analysis. Amgen agreed with the recommendation, and a complete re-read of scans was completed by a BICR group that was composed of radiologists who did not participate in the original reads.

The primary analysis in CodeBreaK 200 was based on this complete, independent, re-read of all scans.

5.1.11.3 Early Withdrawal in the Docetaxel Group

An imbalance was noted in the early withdrawal rates between treatment groups: 23 of 174 patients (13%) who were randomized to the docetaxel group did not receive treatment (randomized-but-not-treated) and discontinued the study, in comparison with 2 of 171 patients (1%) in the sotorasib group. Of the 23 randomized-but-not-treated

patients in the docetaxel group, the end of study reasons were consent withdrawal (20 patients), death (1 patient), investigator decision (1 patient), lost to follow-up (1 patient). Of the 23 patients, 21 ended study within the first 2 weeks following randomization, 1 ended study due to death on day 44 and the other ended study due to study completion on day 2. Subsequent off-protocol therapies were not known for 20 patients who withdrew consent, but 1 of the other 3 did receive subsequent non-platinum chemotherapy. Of these 23 patients, death was recorded for 3 patients on the vital status form (per protocol, investigators were permitted to update survival status from registries, public records, etc. even after a patient had withdrawn from the study, as permitted by local regulations).

The demographics and baseline characteristics of the patients who were randomized but not treated were examined. A stratified Cox model adjusting for baseline covariates was performed as a sensitivity analysis. To evaluate whether the PFS treatment effect is robust under the impact of differential early censoring in the treatment groups, Amgen replaced the early withdrawal patients in the docetaxel group with the imputed data from resampling among those patients in the same treatment group and same stratum (eg, number of prior lines of therapy and history of CNS involvement) who have had at least 6 weeks follow-up for PFS. The results show that the imbalance in early withdrawal did not change the observed treatment effect of sotorasib. Details of these analyses are described below.

5.1.11.3.1 Covariate-Adjusted Analysis

In CodeBreaK 200, there were 23 randomized-not-treated patients in the docetaxel group vs 2 randomized-not-treated patients in the sotorasib group. The differential proportions of early withdrawals may have resulted in an imbalance of baseline characteristics from randomization. Therefore, the stratified Cox model adjusting for additional covariates was performed as a sensitivity analysis for PFS. The covariates were selected using clinical considerations as well as adequate prevalence (at least 10%). This resulted in the selection of the following covariates: liver metastasis (Y, N), baseline tumor burden (> median SLD, ≤ median SLD), ECOG at screening (0, 1), age (≤ 65, < 65), region (North America, rest of world).) The analysis was performed including all 5 covariates. Additionally, covariates related to prognostics were further selected by fitting a stratified Cox model without treatment term using stepwise selection

method with alpha to enter = 0.15 and alpha to stay = 0.10. Three covariates were selected: liver metastasis, baseline tumor burden, ECOG at screening.

The model results are shown in Table 15. In the model with all covariates, the HR was 0.60 (95% CI: 0.46, 0.79), and in the model with selected covariates, the HR was 0.61 (95% CI: 0.47, 0.80). Both covariate-adjusted stratified Cox models favor sotorasib, and this analysis demonstrates the robustness of the PFS outcome.

Table 15. Sensitivity Analysis (CodeBreaK 200): Covariate-adjusted Stratified Cox Model for PFS

Stratified Cox Model = Treatment + Covariates	HR (95% CI)	Descriptive p-value
Model with all covariates		
Treatment (sotorasib vs. docetaxel)	0.60 (0.46, 0.79)	<0.001
Covariates		
Liver metastasis (Y vs N)	1.42 (0.96, 2.11)	0.081
Baseline tumor burden (>mSLD vs <=mSLD)	1.69 (1.245, 2.30)	<0.001
ECOG (1 vs 0)	1.64 (1.20, 2.24)	0.002
Age (>=65 vs <65)	0.845 (0.63, 1.13)	0.25
Region (North America vs rest of world)	0.77 (0.52, 1.14)	0.19
Model with selected covariates		
Treatment (sotorasib vs. docetaxel)	0.61 (0.47, 0.80)	<0.001
Covariates		
Liver metastasis (Y vs N)	1.46 (0.99, 2.15)	0.054
Baseline tumor burden (>mSLD vs <=mSLD)	1.76 (1.30, 2.37)	< 0.001
ECOG (1 vs 0)	1.53 (1.14, 2.06)	0.004

mSLD = median of sum of diameters in target lesions, i.e. 71 mm
Source: Modified from Table 90920230731-04.14.1 and Table 90920230731-4.14.2 of CodeBreaK 200 Primary Analysis

5.1.11.3.2 Imputation for Early Withdrawal in the Docetaxel Group

As noted, in CodeBreaK 200, differential early withdrawal between the 2 treatment groups was observed to have occurred among patients who were randomized and not treated or prematurely discontinued the treatment after a very short period of follow up.

Randomized-not-treated: There were 23 patients in the docetaxel group who were not treated after randomization compared with 2 patients in the sotorasib group. In the PFS primary analysis, among the 23 untreated patients in the docetaxel group, 20 of them were censored at the randomization date; the other 3 patients died at 1.4 to 2.7 months and contributed to PFS events at their death dates.

Early Censoring: Early censoring is defined as being censored before 6 weeks which corresponds to the time scheduled for the first tumor assessment scan. In the docetaxel group, there were 12 treated, early censored patients before 6 weeks vs 4 patients in the sotorasib group.

To evaluate whether the PFS treatment effect is robust under the effect of differential early censoring in the treatment groups, Amgen replaced the early withdrawal patients in the docetaxel group with the imputed data from resampling among those patients in the same treatment group and same stratum (eg, number of prior lines of therapy and history of CNS involvement) who had at least 6 weeks follow-up for PFS. It is noted that 19 patients had progressed or died in the docetaxel group before 6 weeks, and at 6 weeks there were 120 enriched patients from which resampling was performed. Race (Asian vs Non-Asian) was not used as a stratification factor for resampling due to the small sample size of the Asian category. The early withdrawals in the sotorasib group were left as-is, with no imputation for enrichment as a conservative consideration. Therefore, this resampling procedure favors “improved outcome” in the patients in the docetaxel treatment group.

The imputation was performed 20 000 times. In each imputation, the Cox model was applied using imputed data to calculate the HR with 95% CI and the stratified log-rank test was performed to obtain a testing p-value. The number of times (out of 20 000 imputations) that the testing p-value was less than the protocol pre-specified cutoff for PFS primary analysis after adjusting for multiplicity is summarized. In addition, the average estimated HRs and average upper and lower bounds of the 95% CI (antilog of the mean of log HR, 95% CI upper and lower bounds) is described. Empirical 95% CI of estimated HRs are also summarized for reference and results are shown in Table 16. In more than 97% of times out of 20 000 imputations for early withdrawals, the PFS results showed that statistical significance was maintained with an average HR of 0.70. This imputation by resampling patients who withdrew early from the docetaxel group with enriched data from treated patients with longer follow-up in the same treatment group and stratum, further confirms the robustness of the PFS treatment effect for sotorasib compared with docetaxel.

Table 16. Sensitivity Analysis (CodeBreaK 200): Simulation Results for Imputation by Resampling

Patients in Docetaxel Group to be Imputed	Proportion of Times Showing PFS Statistical Significance ($p < 0.044$)	Average HR	HR 95% CI
23 randomized-not-treated[a]	99.1%	0.70	(0.54, 0.90) Empirical (0.66, 0.74)
23 randomized-not-treated[a], and 12 treated and early censored before 6 weeks	97.7%	0.70	(0.54, 0.90) Empirical (0.65, 0.76)

[a] Patients in the docetaxel group who were not treated, including early deaths, were also imputed
Source: userdata/stat/amg510/onc/20190009/docs/stats/RTQ/FDA_memo_stats_programs/Imputation by Resampling/Source
Source: adam.adtte, adam.adsl

5.1.11.4 Informative Censoring Based on Switch to New Anti-Cancer Therapy

Per protocol Amendment 3, Investigator-assessed disease progressions were to be centrally confirmed before the investigator switched the patient to another anticancer therapy. This measure was implemented to minimize informative-censoring in the BICR-assessed PFS endpoint. However, 24 patients in the sotorasib group and 31 patients in the docetaxel group were censored in the BICR analyses owing to investigators switching patients to other anticancer therapy prior to central confirmation of progression.

Amgen performed a pre-specified sensitivity analysis treating the start of a new anticancer therapy as a PFS event. This sensitivity analysis resulted in a HR (95% CI) for the prespecified PFS endpoint of 0.60 (0.47, 0.76) (Figure 7). The result showed that the informative censoring introduced by investigators starting the new anti-cancer therapy before central confirmation of progression did not affect the outcome and result of the study.

5.1.11.5 Effect of Scan Interval on PFS

Disease progression was determined using radiologic scans with BICR assessment of progression per RECIST 1.1 criteria. The imaging interval in this study (ie, every 6 weeks until week 49 and then at 9-week intervals thereafter with +/- 1 week window) was selected to balance the need to monitor progression regularly with patient considerations including logistical issues, convenience, and exposure to radiation.

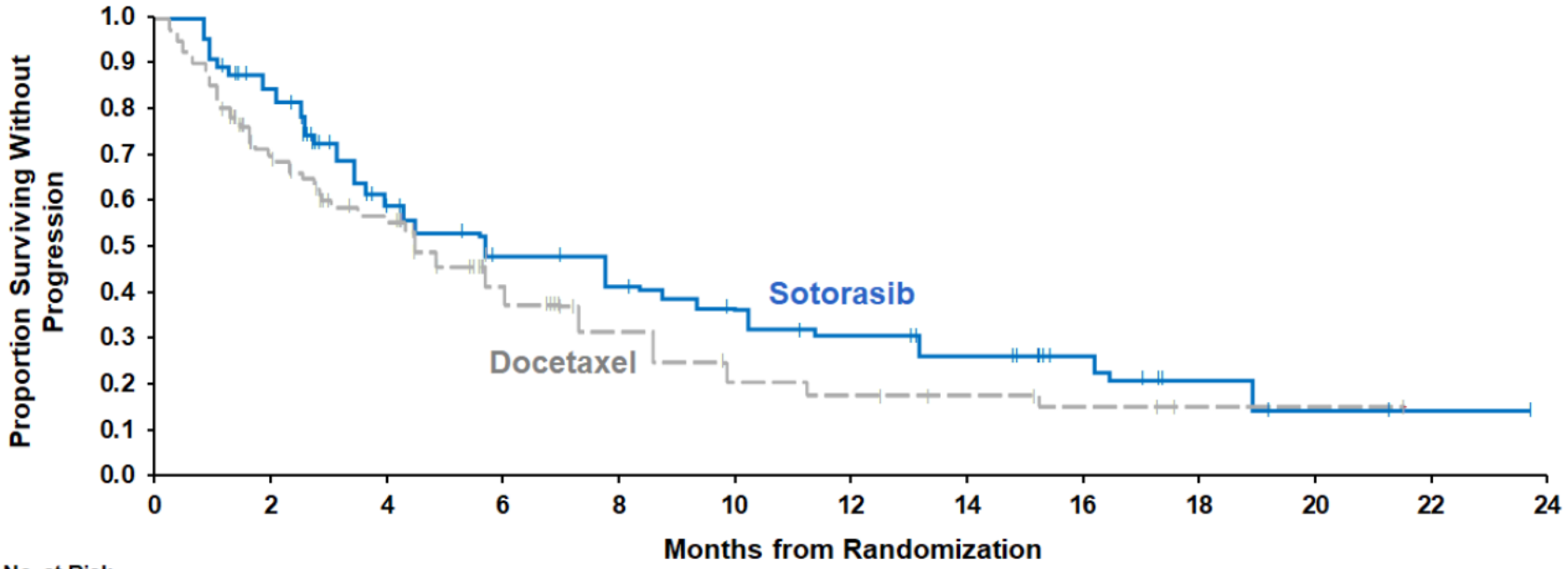
To assess the observation that the median PFS difference is less than the scan interval, a sensitivity analysis was performed using the interval censoring method. Because the tumor assessment is only performed at pre-specified time intervals, the time of disease progression cannot be precisely measured. As an alternative to the PFS primary analysis assigning the event date at the scan date with progressive disease assessment outcome, the interval-censoring method was used to analyze the PFS endpoint as shown in Table 17. The Kaplan Meier curve is provided in Figure 16. This sensitivity analysis based on interval-censored data showed consistent results, confirming superiority of sotorasib over docetaxel in CodeBreaK 200.

Table 17. Sensitivity Analysis (CodeBreaK 200): Interval Censoring Method for PFS

Median PFS (95% CI)		
Sotorasib	**Docetaxel**	**PFS HR (95% CI)**
4.47 (3.94, 7.75)	4.30 (2.86, 4.83)	0.720 (0.550, 0.941)

Source: Modified from Table 90920230628-4.4.2 of CodeBreaK 200 Primary Analysis

Figure 16. Kaplan Meier Curves for PFS Using Interval Censoring Method



No. at Risk													
Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

PFS = progression-free survival
Source: Modified from Figure 90920230727-4.1.14 of CodeBreaK 200 Primary Analysis

5.1.11.6 Restricted Mean Survival Time (RMST)

A sensitivity analysis for PFS was conducted using the RMST method which compares the average progression free survival time between the 2 treatment groups during a specific follow-up period. The RMST calculates the area under the PFS Kaplan Meier curve up to a specific timepoint, integrating the totality of data over time, and is more reliably estimable than median PFS times or PFS rates at a single timepoint. The non-parametric RMST method is an alternative measure to relax the model assumptions in the Cox proportional hazard method, which in turn provides an additional assessment of robustness of the study findings. Amgen compared the RMSTs between the 2 treatment groups starting from 6 months (a timepoint after median PFS of sotorasib) to 14 months, when at least 8% of patients remained at risk. The RMST differences display a value greater than zero at all these time points and all favor sotorasib, which again confirms the robustness of the PFS benefit (Table 18).

Table 18. Sensitivity Analysis (CodeBreaK 200): Restricted Mean Survival Time Estimates for PFS

Truncated Time Point	Sotorasib (months)	Docetaxel (months)	Difference in RMST (95% CI)	Average RMST difference divided by duration of follow-up (95% CI)
RMST Estimates at 10 months	6.06	5.03	1.03 (0.23, 1.82)	10.0% (2.3%, 18.2%)
RMST Estimates at 12 months	6.61	5.28	1.33 (0.40, 2.27)	11.1% (3.3%, 18.9%)
RMST Estimates at 14 months	7.09	5.48	1.61 (0.53, 2.68)	11.5% (3.8%, 19.1%)

Source: Program:/userdata/stat/amg510/onc/20190009/docs/stats/RTQ/FDA_memo_stats_programs/RMST
Source: adam.adtte

5.1.11.7 Crossover

As of the approval date of protocol amendment 3 (15 February 2021), a total of 220 patients were enrolled in CodeBreaK 200 including 111 patients in the docetaxel group. Implementation of this protocol amendment occurred on rolling basis from March 2021 to May 2022 and varied by region. Enrollment into the study was completed on 26 April 2021 with a total of 345 patients enrolled, including 174 patients in the docetaxel group. The first patient in the docetaxel group who became eligible for and crossed over to the sotorasib group occurred on 21 April 2021. Since that date, an additional

99 patients in the docetaxel group could be eligible for crossover, ie, they are either still receiving docetaxel treatment or have entered long-term follow-up but did not start new anticancer therapy.

As described in Section 5.1.3, 46 patients who were randomized to docetaxel crossed over to sotorasib treatment following confirmed progressive disease (referred to as "crossover patients"). As of the data cutoff date of 02 August 2022, 12 crossover patients (26.1%) were still receiving sotorasib, and 34 crossover patients (73.9%) discontinued sotorasib for the following reasons: disease progression (26 patients [56.5%]); adverse event (3 patients [6.5%]); death (2 patients [4.3%]); other (2 patients [4.3%]); patient request (1 patient [2.2%]). Of the 21 crossover patients (45.7%) who discontinued the study, 17 patients (37.0%) died, and 4 patients (8.7%) withdrew consent.

After crossover from docetaxel, patients received sotorasib for a median (range) of 4.8 (0.6, 14.3) months and 10 crossover patients (22%) achieved an objective response post crossover (Table 19). The safety of these crossover patients is discussed in Section 6.1.14.

Table 19. Clinical Outcomes of Crossover Patients (CodeBreaK 200)

	On-Protocol Crossover Patients (N = 46)
Confirmed ORR post crossover, n (%)	10 (21.7)
Median DOR post crossover (months)	10.61
95% CI	(2.14, NE)
Min, Max (+ for censored)	2.1, 10.6
Median DOR follow-up post crossover (months)	8.51
95% CI	(2.17, NE)
Min, Max (+ for censored)	2.1+, 10.6+
Confirmed and unconfirmed ORR post crossover, n (%)	11 (23.9)
Disease control post crossover, n (%)	35 (76.1)
BOR of PD post crossover, n (%)	8 (17.4)
No disease assessment post crossover, n (%)	3 (6.5)
Median OS since randomization (months)	NE
95% CI	(15.31, NE)
Min, Max (+ for censored)	2.9, 24.0+
Median OS follow-up (months)	16.16
95% CI	(15.93, 17.08)
Min, Max (+ for censored)	2.9+, 24.0

BOR = best overall response; DOR = duration of response; NE = not estimable; ORR = objecitive response rate; OS = overall survival; PD = progressive diseasea.
ORR, disease control, progressed post crossover are derived based on investigator RECIST data post first dose of sotorasib and before treatment beyond progression.
Medians and 95% Cis for DOR and OS are estimated using the Kaplan-Meier method. . 95% CIs are estimated using the method by Klein and Moeschberger with log-log transformation.
Data cut-off date: 02 August 2022.
Source: Modified from Table 90920230719-04.7.1 of CodeBreaK 200 Primary Analysis

5.1.11.8 Conclusions on Potential Sources of Bias in CodeBreaK 200

In summary, the results of CodeBreaK 200 are robust and withstand a wide variety of sensitivity analyses to account for potential sources of bias. All analyses conducted confirm and support the overall finding of this study, which is that the use of sotorasib improves progression free survival in patients with *KRAS p.G12C*-mutated NSCLC.

5.2 Supporting Studies

The efficacy data supporting the supplemental marketing application for conversion to traditional approval focused primarily on results from the confirmatory phase 3 study (CodeBreaK 200), with supporting data provided by a dose comparison study (CodeBreaK 100 phase 2 Part B).

5.2.1 CodeBreaK 100

5.2.1.1 Study Design

CodeBreaK 100 is an ongoing, phase 1/2, open-label study evaluating the safety, tolerability, PK, pharmacodynamics, and efficacy of sotorasib in patients with *KRAS p.G12C*-mutated NSCLC, CRC, and other solid tumor types. This study has 2 phases and each phase has multiple parts (Table 2). The data from CodeBreaK 100 phase 2 that supported the accelerated approval of sotorasib on 28 May 2021 is briefly summarized in Section 3.1. CodeBreaK 100 phase 2 Part B is a randomized substudy to evaluate the safety and efficacy of sotorasib as monotherapy at 960 and 240 mg QD in patients with NSCLC. This study was conducted to address an FDA Post Marketing Requirement to further characterize serious adverse events, including gastro-intestinal toxicity, and compare the safety and efficacy of sotorasib 960 mg daily vs a lower daily dose.

Sotorasib has demonstrated a non-linear PK profile, with responses noted at all dose levels ranging from 180 to 960 mg. While 960 mg QD was demonstrated to be safe and effective, this study investigated whether a lower dose could be as safe and efficacious. Following discussion with FDA, the dose of 240 mg QD was selected for further exploration to characterize its PK, safety, and efficacy.

The primary objective was to evaluate tumor ORR as assessed by a BICR per RECIST v1.1. The prespecified primary analysis occurred 6 months after the last patient enrolled in phase 2, part B (data cutoff 09 September 2022). Updated efficacy results as of 18 January 2023 data cutoff date are summarized below. This provides approximately 4.3 months of additional data (with a median follow-up of 12.3 months for OS) since the primary analysis. Details on the study design and efficacy analyses for CodeBreaK 100 phase 2 Part B are provided in Appendix 3.

5.2.1.2 Study Population

Phase 2 Part B enrolled patients with locally advanced and metastatic NSCLC whose disease had progressed after anti-programmed cell death-1 (PD-1) or anti-PD-L1

immunotherapy (unless contraindicated) and/or platinum-based combination chemotherapy and targeted therapy if actionable oncogenic driver mutations were identified with at least 1 prior line of therapy. Enrolling patients could have ECOG performance scores of ≤ 2 and treated brain metastasis. This patient population was different compared with CodeBreaK 200, where both checkpoint inhibitor and platinum-based chemotherapy were required and patients were required to have EGOG scores of ≤ 1. The full analysis set in CodeBreaK 100 phase 2 part B comprised 209 patients who had been randomized to a dose group (104 patients in the 960 mg group and 105 patients in the 240 mg group). Of these, 208 patients received at least 1 dose of sotorasib (104 patients in each group) and comprise the safety analysis set.

5.2.1.3 Patient Disposition

As of 18 January 2023, most patients had discontinued sotorasib (82.7% discontinued 960 mg sotorasib and 83.8% discontinued 240 mg sotorasib); the most frequently reported reason for sotorasib discontinuation in both dose groups [960, 240 mg]) was disease progression (55.8%, 55.2%) and adverse event (14.4%, 13.3%).

As of 18 January 2023, 49.0% of patients in the 960 mg group and 41.9% of patients in the 240 mg group were continuing participation in the study. Reasons for study discontinuation (960, 240 mg) were death (46.2%, 51.4%), withdrawal of consent 3.8%, 6.7%), and lost to follow-up (1.0%, 0%).

5.2.1.4 Baseline Demographics and Disease Characteristics

A total of 114 men (54.5%) and 95 women (45.5%) were enrolled in CodeBreaK 100 phase 2 Part B. The median age (range) was 65 (40 to 85) years, and most patients were White (82.3%) and not Hispanic/Latino (98.1%). Of 104 randomized patients to the 960 mg group, 60.6%, 26.0%, 8.7%, and 4.8% had 1, 2, 3, and ≥ 4 prior lines of anticancer therapies, respectively; 76.0% had prior platinum-based chemotherapy and PD-1/PD-L1; 35.6%, 57.7%, and 6.7% had baseline ECOG of 0, 1, and 2, respectively; 26.0% had brain metastasis. Of 105 randomized patients to the 240 mg group, 57.1%, 24.8%, 9.5%, and 7.6% had 1, 2, 3, and ≥ 4 prior lines of anticancer therapies, respectively; 69.5% had prior platinum-based chemotherapy and anti-PD-1/PD-L1; 35.2%, 56.2%, and 8.6% had baseline ECOG of 0, 1, and 2, respectively; 22.9% had brain metastasis.

5.2.2 Efficacy Results

An overall summary of key efficacy results from CodeBreaK 100 phase 2 Part B (with select efficacy results updated as of 23 June 2023) is provided in Table 20. The updated efficacy results are consistent with the primary analysis results (data cutoff 09 September 2022) and the 90-day update (data cut off 18 January 2023), and show that treatment with sotorasib 960 mg monotherapy continues to demonstrate a clinically meaningful and durable objective response among patients with NSCLC, with an ORR of 32.7% [95% CI: 23.8, 42.6] in 960 mg group and 24.8% (95% CI: 16.9, 34.1) in 240 mg group (Table 20). Median PFS (95% CI) per BICR was 5.39 (4.17, 6.93) months in the 960 mg group and 5.55 (4.14, 8.31) months in the 240 mg group. The stratified Cox HR for 960 vs 240 mg was 0.95 (95% CI: 0.66, 1.36).

With the increased follow-up time in this analysis, the median DOR was estimable in the 960 mg group, with a median DOR of 13.8 (95% CI: 5.6, not estimable) months for the 34 objective responders in the 960 mg group, and 12.5 (95% CI: 7.0, not estimable) months for the 26 objective responders in the 240 mg group.

The OS results as of 23 June 2023 show that there is a trend in survival favoring the 960 mg dose group: the median OS was 13.0 months in the 960 mg group and 11.7 months in the 240 mg group. Treatment with sotorasib 960 mg showed a 1.3-month improvement in median OS and a 25% reduction in hazard of death (HR = 0.75, 95%CI: 0.53, 1.07) compared with the 240 mg group. At the time of last follow up, 27.6% and 37.5% of patients in the 240 and 960 mg groups, respectively, were alive, remained on study, and were censored for OS analysis.

5.3 Overall Summary of Efficacy

In CodeBreaK 200, treatment with sotorasib demonstrated improved PFS and rapid, durable responses for orally administered sotorasib over IV docetaxel in a post-platinum chemotherapy/immunotherapy-treated study population, confirming the clinical benefit demonstrated in the original marketing application based on CodeBreaK 100 phase 2 Part A.

As of a data cut off of 02 August 2022 CodeBreaK 200 showed:

- The study met its primary endpoint: sotorasib lowered the risk of disease progression or death compared with docetaxel: the HR for PFS was 0.663 (95% CI: 0.509, 0.864*; p* = 0.003). The median PFS as assessed by central review was 5.6 months (95% CI: 4.3, 7.8) in the sotorasib group compared with 4.5 months (95% CI: 3.0, 5.7) in the docetaxel group demonstrating a 34% reduction in the risk of progression or death compared with docetaxel.
- More than twice as many patients in the sotorasib group were alive without progression at a 1-year landmark compared with docetaxel (1-year PFS was 24.8% for sotorasib vs 10.1% for docetaxel), and the PFS benefit was consistent across all relevant subgroups, including history of CNS involvement and liver metastasis at baseline.
- Administration of 960 mg sotorasib results in rapid, durable tumor response rates and consistent PFS benefit across subgroups in the randomized phase 3 confirmatory study CodeBreaK 200.
- The effects of sotorasib on PFS were robust: PFS was consistent between BICR and investigator assessment; pre-specified sensitivity analyses with alternative censoring rules showed results were consistent with the primary analysis; additional sensitivity analyses addressing several observations in the PFS primary analysis, including scan intervals and differentiated randomized-not-treated and early censoring, confirmed the PFS effect.
- Sotorasib significantly improved ORR (28.1%; 95% CI: 21.5, 35.4) vs docetaxel (13.2%; 95% CI: 8.6,19.2) ($p < 0.001$), confirming the ORR benefit observed based on the CodeBreaK 100 phase 2 data that supported the original marketing application.
- Responses to sotorasib were durable: the median DOR was 8.6 months (95% CI: 7.1, 18.0) for patients in the sotorasib group vs 6.8 months (95% CI: 4.3, 8.3) for patients in the docetaxel group.
- Sotorasib increased the DCR: 82.5% for sotorasib vs 60.3% for docetaxel.
- Rapid responses to sotorasib were observed: the TTR among the patients in the sotorasib group was half of that for patients in the docetaxel group (median of 1.4 vs 2.8 months, respectively).
- The OS was not significantly different between treatment groups (median of 10.64 months (95% CI: 8.94, 13.96) in the sotorasib group vs 11.30 months (95% CI: 9.00, 14.85) in the docetaxel group (HR = 1.010; 95% CI: 0.766, 1.331; $p = 0.94$). The updated HR for OS at the time of the 90-day safety update was 0.957 (95% CI: 0.741, 1.235).

- Based on PRO assessments, sotorasib was better tolerated, showed clinically meaningful stabilization of QoL measures, and delayed deterioration for global health status, physical functioning, dyspnea, and cough vs docetaxel.
- The exploratory endpoints of PFS2 and time to progression of CNS disease favored sotorasib vs docetaxel.

Supportive Efficacy Results

- Supporting data was provided by CodeBreaK 100 phase 2 Part B, where treatment with sotorasib 960 and 240 mg QD monotherapy demonstrated a clinically meaningful objective response among patients with advanced NSCLC, with similar PFS, numerically higher ORR, and trending improvement in median OS in patients receiving 960 mg sotorasib vs 240 mg sotorasib.
- The ORR results observed in CodeBreaK 100 phase 2 part B were consistent with those observed in the sotorasib group of CodeBreaK 200, (Table 20, which shows CodeBreaK 100 phase 2 part B and CodeBreaK 200 results side by side), and also with the ORR results from the CodeBreaK 100 phase 2 part A results that supported the accelerate approval (ORR = 36.3% (95% CI: 27.8, 45.4)).

As of a data cut off of 23 June 2023 CodeBreaK 100 phase 2 part B showed:

- An ORR of 32.7% (95% CI: 23.8, 42.60 in 960 mg group compared with 24.8% (95% CI: 16.9, 34.1) in 240 mg group.
- Median PFS (95% CI) per BICR of 5.39 (4.17, 6.93) months in the 960 mg group and 5.55 (4.14, 8.31) months in the 240 mg group. The stratified Cox HR for 960 vs 240 mg was 0.950 (95% CI: 0.662, 1.363).
- Median DOR of 13.8 (95% CI: 5.6, not estimable) months for the 34 objective responders in the 960 mg group compared with 12.5 (95% CI: 7.0, not estimable) months for the 26 objective responders in the 240 mg group.
- OS data demonstrating that treatment with 960 mg QD sotorasib showed a 1.3-month longer median OS and a 25% reduction in the hazard (rate) of death when compared with 240 mg QD sotorasib.

These data demonstrate a consistent and meaningful clinical benefit observed across studies, endpoints, and prespecified subgroups.

Table 20. Overall Summary of Results for Efficacy Endpoints Across Key Studies with Updated Results for Select Endpoints

	CodeBreaK 100 phase 2 Part B (Data Cutoff Date: 18 January 2023)[a] **(Data Cutoff 23 June 2023)**		CodeBreaK 200 (Data Cutoff 02 August 2022)[b] **(Data Cutoff 18 January 2023)[a]**	
	Sotorasib 240 mg (N = 105)	Sotorasib 960 mg (N = 104)	Sotorasib 960 mg (N = 171)	Docetaxel (N = 174)
PFS per BICR				
Number of patients with a PFS event – n (%)	61 (58.1) **64 (61.0)**	64 (61.5) **68 (65.4)**	122 (71.3)	101 (58.0)
Median in months (95% CI)	5.6 (4.1, 8.3) **5.6 (4.1, 8.3)**	5.4 (4.2, 6.9) **5.4 (4.2, 6.9)**	5.62 (4.27, 7.75)	4.47 (3.02, 5.68)
Hazard ratio (95% CI)	0.95 (0.66, 1.36) (960 vs 240 mg) **0.95 (0.66, 1.36) (960 vs 240 mg)**		0.66 (0.51, 0.86)	
OS				
Number of events (%)	54 (51.4%) **69 (65.7%)**	48 (46.2%) **60 (57.7%)**	109 (63.7) **121 (70.8)**	94 (54.0) **111 (63.8)**
Median in months (95% CI)	11.7 (9.5, 15.8) **11.7 (9.5, 15.4)**	13.0 (10.8, NE) **13.0 (10.7, 18.8)**	10.64 (8.94, 13.96) **10.64 (8.94, 13.96)**	11.30 (9.00, 14.85) **11.30 (8.84, 15.08)**
Hazard ratio (95% CI)	0.76 (0.51, 1.12) **0.75 (0.53, 1.07)**		1.01 (0.766, 1.33) **0.96 (0.74, 1.24)**	
ORR (95% CI)	24.8% (16.9, 34.1) **24.8% (16.9, 34.1)**	31.7% (23.0, 41.6) **32.7% (23.8, 42.6)**	28.1% (21.5, 35.4) **28.1% (21.5, 35.4)**	13.2% (8.6, 19.2) **13.2% (8.6, 19.2)**
Median DOR (95% CI) months	9.9 (6.9, NE) **12.5 (7.0, NE)**	NE (5.6, NE) **13.8 (5.6, NE)**	8.64 (7.06, 17.97) **8.64 (7.06, 15.90)**	6.80 (4.27, 8.28) **6.80 (4.27, 8.28)**
DCR (95% CI)	81.9% (73.2, 88.7) **81.9% (73.2, 88.7)**	86.5% (78.5, 92.4) **86.5% (78.5, 92.4)**	82.5% (75.9, 87.8)	60.3% (52.7, 67.7)
Median TTR (range) months	1.4 (1.2, 8.3) **1.4 (1.2, 8.3)**	1.4 (1.2, 6.9) **1.4 (1.2, 11.1)**	1.41 (1.2, 8.3) **1.41 (1.2, 8.3)**	2.76 (1.3,11.3) **2.76 (1.3,11.3)**

Footnotes at the end of this table.

BICR = blinded independent central review; DCR = disease control rate; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TTR = time to response

Hazard ratios in Study 20170543 phase 2 Part B were calculated for 960/240 mg and stratified for randomization stratification factors. Hazard ratio < 1.0 indicated a lower risk and longer time-to-event for 960 mg relative to 240 mg.

Endpoints without updated data cuts at the most recent cutoff date were not reported as the endpoint was mature in previous data cut.

[a] 90-day safety update

[b] primary analysis

Source: Modified from Table 14-4.3.1, Table 14-4.2.1, Table 14-4.2.3, and Table 14-4.1.1 of Study 20170543 phase 2 Part B Supplemental CSR; Table 14-4.1,Table 4-4.5.12, Table 4-4.2.1 and Table 14-4.3.1 of CodeBreaK 200 Primary Analysis; Table 7-2, Table 7-3, and Table 7-6 of Study 20170543 phase 2 Part B Supplemental Interim Analysis 2 CSR; Table 14-4.3.1 of CodeBreaK 200 90-day Safety Update

6. Safety

Results from analyses of the following data and cutoff dates are summarized in this section:

- Data through 02 August 2022 from CodeBreaK 200

For some safety sections, supporting data through 02 August 2022 from an integrated analysis of pooled sotorasib monotherapy data from CodeBreaK 200 and data through 09 September 2022 from CodeBreaK 100 phase 2 Part B, as well as the following sotorasib monotherapy studies (Appendix 8) are included:

- CodeBreaK 100 phase 1 and phase 2 Part A (CodeBreaK 100)
- Study 20190135 (CodeBreaK 101) Subprotocol G
- Study 20190147 (CodeBreaK 105)

6.1 CodeBreaK 200

All safety summaries are based on the safety analysis set (169 patients in the sotorasib group and 151 patients in the docetaxel group who received at least 1 dose of investigational product).

6.1.1 Exposure to Sotorasib

Patients who received sotorasib had a longer duration of treatment than patients who received docetaxel. As of 02 August 2022, for patients in the sotorasib group the (median [range]) duration of treatment was 20 (0.4, 101) weeks administered over 7 (1, 34) 21-day cycles compared with a (median [range]) duration of treatment of 12 (3, 101) weeks administered over 4 (1, 33) 21-day cycles for patients in the docetaxel group. The median duration of treatment with docetaxel in this study population with advanced NSCLC was consistent with published literature (Garon et al, 2014, Takeda et al, 2009; Ko et al, 2007). In the sotorasib group (median [range]) the relative dose intensity was 100% (23.7, 100.0) vs 94.8% (48.9, 105.6) in the docetaxel group.

6.1.2 Adverse Event Data Collection Period and Safety Analyses

Treatment-emergent adverse events (referred to as “adverse events”) are defined as events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if patients crossed over from docetaxel to sotorasib, whichever occurred earlier. The difference in duration of treatment means that the adverse event collection period was approximately 1.7 fold longer for patients in the sotorasib group vs patients in the docetaxel group. For this reason, exposure-adjusted event rates per 100 patient-years were evaluated in an ad hoc analysis, and are presented alongside patient incidence rates in Table 21.

Per protocol, investigators were required to report all known signs and symptoms when an adverse event or serious adverse event was due to NSCLC, while deaths due to disease progression in the absence of signs and symptoms were required be reported as the primary tumor type. In order to allow for a more clinically relevant description of safety, a list of select preferred terms within the Neoplasms system organ class that are reflective of the primary tumor and represent disease progression events were excluded from all safety analyses (excluded disease progression preferred terms are shown in Table 35 in Appendix 6 and a summary of all adverse events and fatal adverse events with all reported preferred terms is shown in Appendix 7).

6.1.3 Overall Adverse Events

A total of 165 patients (97.6%) in the sotorasib group and 148 patients (98.0%) in the docetaxel group had at least 1 adverse event (Table 21). The patient incidences of adverse events, including the combined incidence of grade 3 and 4 adverse events and serious adverse events were similar between treatment groups. Adverse events leading to discontinuation and fatal events were balanced (Table 21 and Section 6.1.9). When adjusted for exposure, the incidences of adverse events for the safety summary categories, with the exception of adverse events leading to interruption, were lower with sotorasib compared to docetaxel. A similar trend of lower adverse events in all the safety summary categories (with the exception grade 1 and grade 3 adverse events, which were similar between treatment groups, and adverse events leading to treatment interruption, which were higher in patients receiving sotorasib) was observed for investigator assessed treatment-related adverse events (Table 34 in Appendix 5).

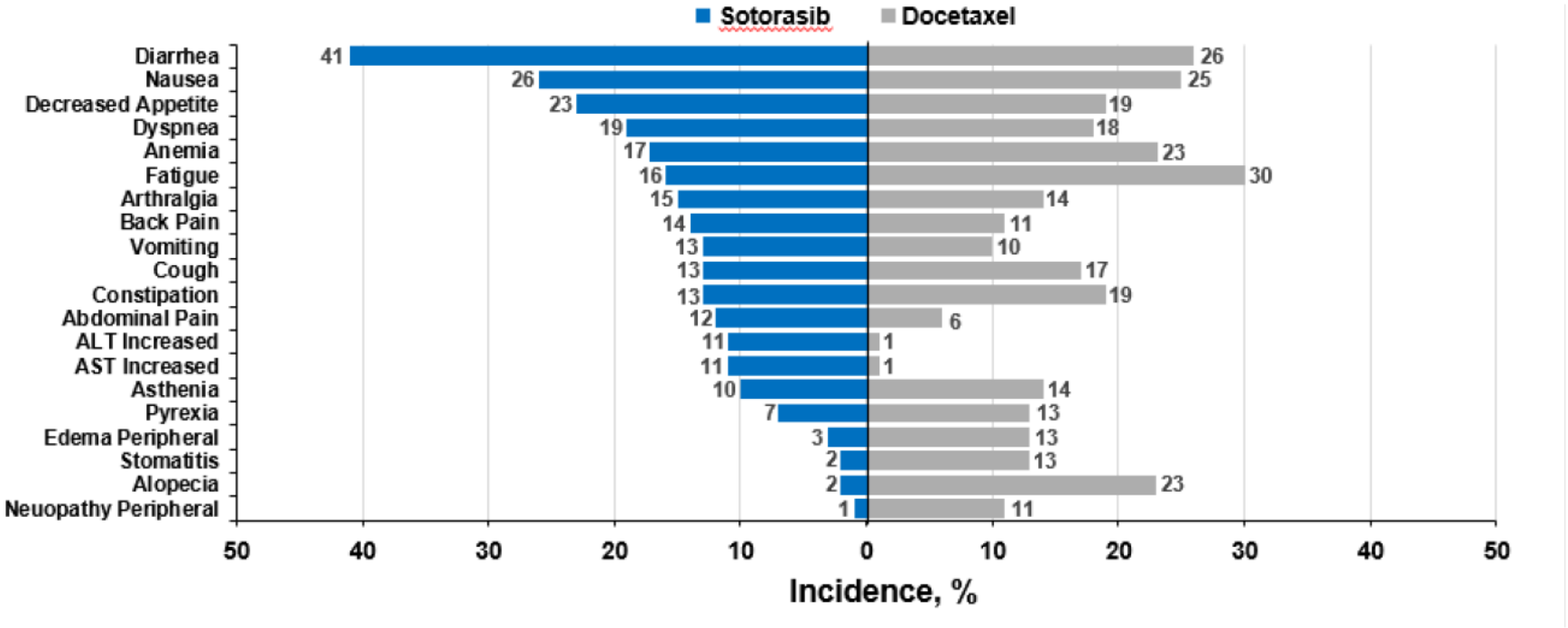
The most frequent adverse events in CodeBreaK 200, defined as those with a patient incidence of 10% or higher for either treatment are shown in Figure 17. Most events for which the incidence is higher (≥ 5%) in patients receiving sotorasib (diarrhea, ALT increased, AST increased, and alkaline phosphatase increased) are all listed as adverse reactions in the prescribing information. Similarly, most events reported at a higher frequency (≥ 5%) in patients receiving docetaxel (fatigue, alopecia, neutropenia, edema peripheral, stomatitis, neuropathy peripheral, and pneumonia) are listed in the prescribing information for that drug. In summary, the types of adverse events observed for sotorasib and docetaxel are differentiated and consistent with the expected safety profile of each drug.

Table 21. Summary of Exposure-adjusted and Patient Incidence Rates of Treatment-emergent Adverse Events - Excluding Select Preferred Terms from Neoplasms System Order Class (Safety Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

	Patient Incidence		Exposure-adjusted	
	Sotorasib (N = 169) n (%)	Docetaxel (N = 151) n (%)	Sotorasib (N = 169) e [r]	Docetaxel (N = 151) e [r]
All treatment-emergent adverse events	165 (97.6)	148 (98.0)	15.7 [1047.7]	6.1 [2443.8]
Grade 1	15 (8.9)	12 (7.9)	94.1 [15.9]	48.4 [24.8]
Grade 2	38 (22.5)	46 (30.5)	87.8 [43.3]	35.6 [129.3]
Grade 3	87 (51.5)	59 (39.1)	72.4 [120.2]	38.0 [155.3]
Grade 4	14 (8.3)	20 (13.2)	102.7 [13.6]	47.3 [42.3]
Grade 3 and 4	101 (59.8)	79 (52.3)	70.5 [143.3]	34.9 [226.5]
Fatal adverse events	11 (6.5)	11 (7.3)	104.7 [10.5]	50.1 [22.0]
Grade ≥ 2	150 (88.8)	136 (90.1)	40.7 [368.5]	12.0 [1130.5]
Grade ≥ 3	112 (66.3)	90 (59.6)	68.4 [163.7]	33.5 [268.4]
Grade ≥ 4	25 (14.8)	31 (20.5)	102.8 [24.3]	47.0 [66.0]
Serious adverse events	80 (47.3)	66 (43.7)	89.3 [89.6]	39.4 [167.4]
Leading to discontinuation of Investigational product	23 (13.6)	23 (15.2)	104.6 [22.0]	49.1 [46.9]
Leading to dose reduction	26 (15.4)	43 (28.5)	86.6 [30.0]	34.9 [123.3]
Leading to dose interruption	84 (49.7)	41 (27.2)	71.9 [116.8]	42.1 [97.3]

e = Sum across all patients, the total time to first event or total exposure if no event (years); N = Number of patients in the analysis set; n = Number of patients with observed data; r = Exposure-adjusted event rate per 100 patient years (n/e-yr*100).
Percentages are based on N
Adverse events coded using Medical Dictionary for Regulatory Activities (version 25.0) and graded using Common Technical Criteria for Adverse Events (version 5.0).
Multiple occurrences of the same event for a patient are counted as single events.
Treatment-emergent adverse events in this table were events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if patients cross over from docetaxel to sotorasib, whichever occurs earlier.
For patients with multiple events under the same category, only the worst grade was reported.
Grade 5 (fatal) adverse events may have started prior to data cutoff and result in death after data cutoff. These events were summarized in this table but the death after data cutoff are not included in analysis.
A list of select preferred terms within the Neoplasms system organ class were excluded from this summary as they represent disease progression events
Data cut-off date 02 August 2022.
Source: Modified from Table 90920230616-6.3 of CodeBreaK *200 Primary Analysis*

Figure 17. Adverse Events of Any Grade Occurring in ≥ 10% of Patients in Either Treatment Group Excluding Select Preferred Terms from Neoplasms System Order Class (Safety Analysis Set) (CodeBreaK 200 PFS Primary Analysis)



PFS = progression-free survival
Incidence is shown by each bar. Only events occurring ≥ 10% of patients in either treatment group are shown.
Data cutoff date: 02 August 2022
Source: Modified from Table 90920230717-6.12.2 of CodeBreaK 200 Primary Analysis

6.1.4 Serious Adverse Events

Serious adverse events occurred in 80 patients (47.3%) in the sotorasib group and 66 patients (43.7%) in the docetaxel group. The most common serious adverse events (≥ 2% patients in either group) are shown in Table 22. The most common seriousness criterion was hospitalization, which was reported in 63 patients (41.7%) in the docetaxel group and 77 patients (45.6%) in the sotorasib group. Most hospitalizations were due to disease progression or other cancer-related complications, and in the sotorasib group fewer patients had treatment-related adverse events resulting in hospitalization compared with the docetaxel group: 15 patients (9%) sotorasib compared with 33 patients (22%) docetaxel. In the sotorasib group, most serious adverse events occurred in 1 patient each, and analysis of these events did not reveal any trends or patterns of a safety concern. Diarrhea is further discussed in Section 6.1.10.4.

Table 22. Most Frequent (≥ 2% Patients in Either Group) Serious Adverse Events by Preferred Term (CodeBreaK 200 Safety Analysis Set)

Preferred Term	Sotorasib N = 169 n (%)	Docetaxel N = 151 n (%)
Diarrhea	5 (3)	2 (1)
Pneumonia	1 (0.6)	10 (7)
Febrile neutropenia	0 (0)	7 (5)
Anemia	1 (0.6)	5 (3)
Dyspnea	2 (1)	4 (3)
Respiratory failure	1 (0.6)	4 (3)
Sepsis	0 (0)	3 (2)

Data Cutoff Date: 02 August 2022

Source: Modified from Table 14-6.4.1 of CodeBreaK 200 Primary Analysis

6.1.5 Grade 3 Adverse Events

In CodeBreaK 200, grade 3 adverse events were reported in 87 patients (51.5%) in the sotorasib group and 59 patients (39.1%) in the docetaxel group. For patients in the sotorasib group, diarrhea and AST/ALT elevations were the most frequently reported grade 3 adverse events, while anemia and fatigue were the most frequently reported grade 3 adverse events for patients receiving docetaxel (Table 23).

Table 23. Most Frequent (≥ 5% in Either Group) Worst Grade of 3 Adverse Events by Preferred Term (CodeBreaK 200 Safety Analysis Set)

Preferred Term	Sotorasib N = 169 n (%)	Docetaxel N = 151 n (%)
Diarrhea	23 (14)	4 (3)
Alanine aminotransferase increased	14 (8)	0 (0)
Aspartate aminotransferase increased	9 (5)	0 (0)
Anemia	8 (5)	9 (6)
Fatigue	4 (2)	9 (6)
Pneumonia	0 (0)	7 (5)
Febrile neutropenia	0 (0)	7 (5)

Data Cutoff Date: 02 August 2022
Source: Modified from Table 14-6.2.3 of CodeBreaK 200 Primary Analysis

6.1.6 Grade 4 Adverse Events

Grade 4 adverse events were reported in 14 patients (8.3%) in the sotorasib group and 20 patients (13.2%) in the docetaxel group. The most common grade 4 events in the sotorasib group were hepatic adverse events (discussed in Section 6.1.10.1). In the docetaxel group, the most common grade 4 adverse event was neutropenia (Table 24).

Table 24. Most Frequent (≥ 1% in Either Group) Worst Grade of 4 Adverse Events by Preferred Term (CodeBreaK 200 Safety Analysis Set)

Preferred Term	Sotorasib N = 169 n (%)	Docetaxel N = 151 n (%)
Neutropenia	0 (0.0)	8 (5.3)
Neutrophil count decreased	0 (0.0)	5 (3.3)
Drug-induced liver injury	2 (1.2)	0 (0.0)
Hepatotoxicity	2 (1.2)	0 (0.0)
Pneumonia	0 (0.0)	2 (1.3)
White blood cell count decreased	0 (0.0)	2 (1.3)
Respiratory failure	0 (0.0)	2 (1.3)

Data Cutoff Date: 02 August 2022
Source: Modified from Table 14-6.2.3 of CodeBreaK 200 Primary Analysis

6.1.7 Fatal Adverse Events

After excluding preferred terms related to disease progression, fatal adverse events were reported for 11 patients (6.5%) in the sotorasib group and 11 patients (7.3%) in the docetaxel group (Table 21). Review of fatal adverse events did not show evidence of any pattern or trend to suggest increased risk of death due to toxicity (See Section 6.1.8).

6.1.8 All Deaths

The CodeBreaK 200 protocol was designed to continuously collect the survival status of patients after they discontinue treatment through long-term follow-up (as long as patients did not withdraw from the study and their data collection through public record was permitted by local law). These additional deaths are included in the OS analysis, which is mature, and does not suggest any detriment to survival for sotorasib treatment with HR = 0.957 (95% CI: 0.741, 1.235) (Figure 9).

Amgen reviewed all deaths occurring in CodeBreaK 200 to distinguish those due to disease progression from those due to other adverse events. As described in Section 6.1.2, investigators were only required to report disease progression events as adverse events during the treatment-emergent adverse event reporting period (from first dose of investigational product through 30 days after the last dose and before crossover, whichever occurred earlier); death reported after the treatment-emergent adverse event reporting period were thus mostly captured on the end-of-study case report form. Deaths collected from public-records after a patient ended study may be without any documented cause and were captured as cause of death unknown. Adverse events that were reported as any of the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (Table 35 in Appendix 6) related to the underlying malignancy, or where the investigator reported disease progression as cause of death on the end-of-study case report form, were categorized as death due to disease progression. If an adverse event was reported as a sign or symptom of disease progression, and cause of death was reported as disease progression, the fatal event was considered as due to disease progression.

An accounting of all deaths in CodeBreaK 200 (107 patients [63.3%]) sotorasib and 89 patients [58.9%] docetaxel) is provided in Table 25. This includes the following:

- Fatal adverse events recorded during the treatment-emergent adverse event collection period (within 30 days of last dose of investigational product), including deaths due to disease progression and other fatal adverse events.
  - All fatal events were considered by the investigators to be unrelated to study treatment except single event of ILD in the sotorasib group and multiple organ dysfunction syndrome and ileus in the docetaxel group. Fatal treatment-emergent adverse events are discussed in Section 6.1.7.
- Fatal events that were not treatment-emergent (occurred during the long-term follow-up period and > 30 days after last dose of investigational product); these were mostly related to disease progression.

Table 25. Summary of Deaths in Treated Patients (Safety Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

	Sotorasib (N = 169)	Docetaxel (N = 151)
Total deaths of any cause - N1	107	89
Related to disease progression - n/N1 (%)	90 (84.1)	72 (80.9)
Non disease progression - n/N1 (%)	11 (10.3)	11 (12.4)
Unknown - n/N1 (%)	6 (5.6)	6 (6.7)
Fatal events within 30 days of last dose of investigational product - n	37	18
Related to disease progression - n	28	13
Non disease progression - n	8	5
Unknown - n	1	0
Fatal events occurring >30 days after last dose of investigational product[a] - n	55	54
Related to disease progression - n	51	47
Non disease progression - n	3	6
Unknown - n	1	1
Deaths reported without fatal AE records - n	15	17
Related to disease progression - n	11	12
Non disease progression - n	0	0
Unknown - n	4	5

CRF = case report form; N = Number of patients in the analysis set; N1 = Number of patients with all-cause death; n = Number of patients; PFS = progression-free survival
Treatment-emergent period was from the first dose of any study treatment to the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if patients cross over from docetaxel to sotorasib, whichever occured earlier.
Disease progression related deaths were flagged based on either fatal adverse events preferred term or primary cause of death reported on End of Study CRF. Deaths collected from public-record after patient ended study may have been without any documented cause.
Adverse events were coded using Medical Dictionary for Regulatory Activiites (version 25.0).
[a] these were deaths recorded after the 30-day treatment-emergent adverse event window
Data cut-off date = 02 August 2022.
Source: Modified from Table 90920230712-06.8.1 of CodeBreaK 200 Primary Analysis

The above table shows that the primary cause of death for the majority of patients was disease progression and this accounted for 90 (84.1%) and 72 (80.9%) of deaths in the sotorasib and docetaxel groups, respectively. Deaths due to other adverse events accounted for 11 (10.3%) of sotorasib deaths and 11 (12.4%) of docetaxel deaths (Table 26).

Upon review of the individual fatal adverse events in the sotorasib group (Table 26), it was determined that most occurred in the setting of disease progression, including a fatal event ILD in 1 patient that was considered by the investigator as related to sotorasib, but the cause of death was reported as “massive disease progression”

(see Section 6.1.10.2). Additionally, there were 4 fatal adverse events not directly associated with disease progression including COVID-19 pneumonia, delirium (in the setting of a recent stroke), acute kidney injury (see Section 6.1.10.3) and colitis. The fatal event of colitis occurred 4 weeks after sotorasib was discontinued due to disease progression and subsequent to the start of docetaxel (administered outside of the clinical trial); the event was attributed to docetaxel toxicity by the investigator.

Table 26. Fatal Events by Preferred Terms (Excluding Disease Progression-related Preferred Terms) (Safety Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

Preferred Term	Sotorasib (N = 169) n (%)	Docetaxel (N = 151) n (%)
Respiratory failure	1 (0.6)	3 (2.0)
Multiple organ dysfunction syndrome	1 (0.6)	1 (0.7)
Acute kidney injury	1 (0.6)	0 (0.0)
COVID-19 pneumonia	1 (0.6)	0 (0.0)
Colitis	1 (0.6)	0 (0.0)
Delirium	1 (0.6)	0 (0.0)
Disseminated intravascular coagulation	1 (0.6)	0 (0.0)
Dyspnoea	1 (0.6)	0 (0.0)
Interstitial lung disease	1 (0.6)	0 (0.0)
Lung disorder	1 (0.6)	0 (0.0)
Pneumonia	1 (0.6)	0 (0.0)
Altered state of consciousness	0 (0.0)	1 (0.7)
Aspiration	0 (0.0)	1 (0.7)
COVID-19	0 (0.0)	1 (0.7)
Cerebrovascular accident	0 (0.0)	1 (0.7)
Ileus	0 (0.0)	1 (0.7)
Pulmonary embolism	0 (0.0)	1 (0.7)
Respiratory distress	0 (0.0)	1 (0.7)
Total	11	11

N = Number of patients in the analysis set; n = Number of patients with observed data;
PFS = progression-free survival
Disease progression related deaths were flagged based on either fatal adverse events preferred term or primary cause of death reported on End of Study CRF.
Adverse events are coded using Medical Dictionary for Regulatory Activiites (version 25.0)
Data cut-off date 02 August 2022.
Source: Modified from Table 90920230712-6.8.2 CodeBreaK 200 Primary Analysis

6.1.9 Adverse Events Leading to Dose Reduction/Interruption

Dose Reduction or Interruption

The patient incidence of adverse events leading to dose reduction were lower in the sotorasib group than the docetaxel group, and the patient incidence of dose interruptions due to adverse events were higher in the sotorasib group than the docetaxel group (Table 21). Per protocol, up to 2 dose reductions were allowed for either sotorasib or docetaxel and drug was to be discontinued, temporarily delayed, or dosage temporarily reduced, in the event of a toxicity that, in the opinion of the investigator, warranted the discontinuation or dose reductions, per dose modification guidelines. Of note, docetaxel was administered once Q3W as an IV infusion, while dosing of sotorasib is administered daily by mouth, resulting in 21 sotorasib administrations vs 1 docetaxel administration per 3-week period.

The most frequently reported adverse events that led to dose reduction of investigational product (≥ 2% of patients in either group) were diarrhea (14 patients [8.3%]) and ALT increased (6 patients [3.6%]) in the sotorasib group; and neutropenia (7 patients [4.6%]), fatigue (6 patients [4.0%]), asthenia (5 patients [3.3%]), febrile neutropenia and peripheral neuropathy (4 patients [2.6%] each), and diarrhea and nausea (3 patients [2.0%] each) in the docetaxel group. The most frequently reported adverse events that led to dose interruption of investigational product (≥ 2% of patients in either group) were diarrhea (26 patients [15.4%]), ALT increased (10 patients [5.9%]), AST increased (9 patients [5.3%]), nausea (8 patients [4.7%]), decreased appetite (5 patients [3.0%]), and abdominal pain upper (4 patients [2.4%]) in the sotorasib group; and pneumonia (7 patients [4.6%] each), fatigue (5 patients [3.3%]), and COVID-19 (3 patients [2.0%]) in the docetaxel group.

In summary, the most common adverse events leading to dose interruption or reduction were consistent with the known safety profiles of the individual study treatments. Dose reductions and interruptions are the primary means of managing sotorasib risks.

Treatment Discontinuation

As of 02 August 2022, the patient incidence of adverse events leading to discontinuation were similar for both treatment groups (Table 21). The most common adverse events that led to discontinuation of investigational product (reported for ≥ 3 patients in either group) were ALT increased (6 patients [3.6%]) and blood bilirubin increased (4 patients [2.4%]) in the sotorasib group; and fatigue (3 patients [2.0%]) in the docetaxel group.

The majority of adverse events leading to treatment discontinuation in the sotorasib group occurred in 1 patient and there were no other notable or concerning trends.

6.1.10 Adverse Events of Interest

Hepatotoxicity, renal toxicity, and ILD/pneumonitis were prespecified as event of interests (EOIs) for sotorasib based on emerging clinical study data and/or nonclinical data.

6.1.10.1 Hepatotoxicity

Though nonclinical data did not predict potential for sotorasib hepatotoxicity in human studies, emerging clinical data in the lung program suggested that this was a risk with sotorasib. In CodeBreaK 200, hepatotoxicity adverse events were reported for 41 patients (24.3%) in the sotorasib group (Table 27). In the sotorasib group, reported hepatic adverse events were characterized by abnormal liver function tests and the most common adverse events (≥ 2% of patients) were ALT increased and AST increased (18 patients [10.7%] each), and gamma-glutamyltransferase increased and blood bilirubin increased (5 patients [3.0%] each).

Most hepatic events in the sotorasib group were grade ≥ 3 in severity. Of note, according to CTCAE version 5.0, for transaminase and alkaline phosphotase elevations, grade 3 corresponds to levels that are 5 to 20 times the upper limit of normal (ULN) and for bilirubin, levels that are 3 to 10 times ULN.

Grade ≥ 3 hepatotoxicity adverse events were reported for 32 patients (18.9%) in the sotorasib group, the most common (≥ 2% of patients) of which were ALT increased (14 patients [8.3%]) and AST increased (10 patients [5.9%]). Serious adverse events were reported for 10 patients (5.9%) in the sotorasib group, including 2 events of drug induced liver injury and 1 event of hepatic failure. The 2 events of drug induced liver injury were characterized by abnormal liver function tests: patient 1 had cholestastic hepatitis and portal inflammation; ALT 559 U/L (13 x ULN), AST 438 U/L (13 x ULN), alkaline phosphatase 906 U/L (7 x ULN), and bilirubin 8.6 mg/dl (7 x ULN); patient 2 had ALT 1444 U/L (35 x ULN), AST 953 U/L (24 x ULN), alkaline phosphatase 605 (5 x ULN), and bilirubin 9.74 (8 x ULN). Both patients were hospitalized for the event and treatment permanently withdrawn; events resolved without sequelae.

The patient with hepatic failure had elevations of ALT 165 U/L (4 x ULN), AST 93 U/L (3 x ULN) and ALP 254 UL (2 x ULN) approximately 2 weeks after start of sotorasib. The events resolved and sotorasib was restarted at a lower dose (480 mg) about 2.5

weeks later but the events recurred. Dose was further reduced to 240 mg and the patient remained on that dose until disease progression. There were no reports of severe liver injury with encephalopathy and/or coagulopathy, no fatal events, and no confirmed Hy's law cases in CodeBreaK 200. Hepatotoxicity events were managed by dose interruptions (17.8%), dose reductions (6.5%) and steroids (28 of 41 patients [68.3%]) (Table 27). Median time to onset of hepatic event was 46 days, and in most patients (36 of 41 [87.8%]) all events had resolved at the time of the primary analysis; the median duration of hepatic events was 22 days, and the median duration of treatment interruption was 16 days (Table 27).

Table 27. Summary of Hepatotoxicity Adverse Events of Interest (Safety Analysis Set) (CodeBreaK 200 PFS Primary Analysis)

Event of Interest Category	Sotorasib (N = 169) n (%)
Number of patients reporting EOI (narrow), N	41 (24.3)
Grade 2	5 (3.0)
Grade 3	25 (14.8)
Grade 4	7 (4.1)
Serious	10 (5.9)
Fatal adverse events	0 (0.0)
Patients with fully resolved events -n/N(%)[a]	36 (87.8)
Median time to onset, days	46
Median duration of event, days	22
Median duration of treatment interruption, days	16
Management	
Dose interruption	30 (17.8)
Dose reduction	11 (6.5)
Treatment withdrawn	13 (7.7)
Corticosteroids, n/N (%)	28 (68.3)

EOI = event of interest; N = number of patients in the analysis set; n = number of patients with observed data; PFS = progression-free survival

Treatment-emergent adverse events in this table were events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if patients crossed over from docetaxel to sotorasib, whichever occurred earlier. For patients with multiple events under the same category, only the worst grade was reported. Grade 5 fatal adverse events may have started before data cutoff and resulted in death after data cut-off. These events are summarized in this table, but deaths after data cutoff are not included in analysis.

Hepatotoxicity narrow search strategy: Hepatic Disorders SMQ (Narrow)

[a]7 unresolved hepatic events reported in 5 patients: 3 patients died from disease progression prior to event resolution, 1 patient lost to follow-up, and 1 patient discontinued sotorasib due to hepatic adverse event; no further information reported

Data cut-off date = 02 August 2022.

Source: Modified from Table 14-6.8.1, Table 14a-6.5.19 and Table 14-6.10.4 of CodeBreaK 200 Primary Analysis, Table 20220929-1.2.1, Table 90920230811-6.14.2 of CodeBreaK 200 Primary Analysis and safety data on file.

Maximum shifts for on study laboratory liver tests for patients receiving sotorasib are shown in Table 28. These were consistent with anticipated hepatotoxicity profile of sotorasib.

Table 28. Shift Table For Patient Incidence of Worst On Study Grade for Patients Reveving Sotorasib (N = 169)

Lab Parameter	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase	100 (59.2)	35 (20.7)	6 (3.6)	25 (14.8)	2 (1.2)
Aspartate aminotransferase	103 (60.9)	34 (20.1)	12 (7.1)	18 (10.7)	1 (0.6)
Total bilirubin	149 (88.2)	5 (3.0)	6 (3.6)	7 (4.1)	1 (0.6)
Alkaline phosphatase	103 (60.9)	35 (20.7)	20 (11.8)	10 (5.9)	0 (0%)

Data cutoff date: 02 August 2022
Source: Modified from Table 14-7.2.12, Table 14-7.2.13, Table 14-7.2.2, and Table 14-7.2.4 of CodeBreaK 200 Primary Analysis

Hy's law criteria were defined as ALT or AST > 3 x ULN and total bilirubin > 2 x ULN and ALP < 2 x ULN. Patients with any of these laboratory components occurring within ±30 days of each other were flagged and reviewed for confirmation of Hy's law criteria. Eight patients were suspected to have laboratory values that potentially met Hy's law criteria. Upon review, none of the liver function tests were confirmed to have met Hy's law criteria as ALP was > 2 x ULN at the time of peak ALT, AST, and total bilirubin elevations.

The results from CodeBreaK 200 were consistent with results from an integrated analysis of patients with NSCLC treated at 960 mg QD where hepatotoxicity (narrow search) adverse events of interest were reported for 148 patients (27.0%). The most frequently reported (≥ 5% of patients) hepatotoxicity adverse events of any grade were increased ALT (14.8%) and increased AST (14.6%).

In summary, reports of hepatotoxicity were consistent with those previously observed in the sotorasib program. Management of this risk as per the prescribing information includes monitoring of liver function tests (ALT, AST, ALP, and total bilirubin) prior to the start of sotorasib therapy, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated. Based on severity of adverse reaction, sotorasib should be withheld, or dose reduced, or permanently discontinued.

6.1.10.2 Pneumonitis/Interstitial Lung Disease

While there were no sotorasib-related histopathological observations detected in the lung and there were no histopathologic observations related to ILD in nonclinical studies,

emerging clinical data suggested that this was a risk with sotorasib. In CodeBreaK 200, pneumonitis/ILD adverse events were reported in 4 (2.4%) of patients in the sotorasib group.

In the sotorasib group, 3 patients (1.8%) had pneumonitis and 1 patient (0.6%) had ILD: 1 patient had 2 pneumonitis adverse events, both events were treatment-related, the first event was a grade 3 in severity that led to drug interruption, and the event resolved; the second event was a grade 1 event that led to dose reduction and the event was reported as ongoing. Another patient had grade 2 pneumonitis that was not considered by the investigator as related to treatment, required no treatment modification, and the event resolved. The third patient had grade 1 pneumonitis that was not considered by the investigator as related to treatment, required no dose modification, and the event resolved. The fourth patient had a fatal serious adverse event of ILD that was considered by the investigator as related to treatment. The median time to onset of the ILD event was 42.5 days and median duration of events was 53 days.

The patient with fatal ILD was hospitalized with symptoms of dyspnea, fever and oxygen desaturation. Sotorasib was withdrawn and the patient was treated with steroids due to suspicion of pulmonary fibrosis. A CT scan showed new pleural nodules, growth of target and non-target lesions, pulmonary fibrosis, and massive disease progression. The patient died 25 days after the onset of symptoms and the cause of death was recorded as due to disease progression.

The results from CodeBreaK 200 were consistent with results from an integrated analysis patients with NSCLC treated at 960 mg QD, where pneumonitis (narrow search) adverse events of interest were reported for 13 patients (2.4%). The most frequently reported (≥ 1% of patients) adverse event within this search was pneumonitis (1.8%).

6.1.10.3 Renal Adverse Events

In the nonclinical toxicology studies of sotorasib, the kidney was identified as a target organ of toxicity in the rat but not the dog. Renal toxicity was characterized by degeneration and necrosis of the proximal tubular epithelium localized to the outer stripe of the outer medulla, a site with high levels of metabolizing enzymes, which suggested that renal metabolism was involved. Sotorasib-related renal toxicity observed in the rat is mediated by a nephrotoxic metabolite derived from the mercapturate/β-lyase pathway (Werner et al, 2021). Based on these nonclinical findings, renal adverse events were considered adverse events of special interest for

sotorasib. In CodeBreaK 200, 10 patients (5.9%) in the sotorasib group had renal adverse events. The events were acute kidney injury and renal failure (3 patients [1.8%] each), chronic kidney disease and renal impairment (2 patients [1.2%] each), and toxic nephropathy 1 patient [0.6%]). All but 1 of the renal events were grade 1 to 2 in severity, and there was 1 grade 5 (fatal) event.

The fatal event occurred in a patient who had previously been treated with pembrolizumab and who developed acute renal failure after 3 weeks of sotorasib treatment (cycle 2 D1). Creatinine was elevated at 3.52 mg/dL (baseline was 0.59 mg/dL). The patient had no history of renal dysfunction and a renal ultrasound did not reveal any post-renal etiologies. Per the investigator, a combination of poor oral intake concurrent with diarrhea (grade 1), concomitant omeprazole and diclofenac which, per the reporter, can increase the risk of interstitial nephritis when in combination with immunotherapy, likely contributed to the events. Sotorasib was withheld and dialysis was not performed. The patient developed metabolic acidosis, became anuric, and died 3 days after last dose of sotorasib.

For patients in the the sotorasib group, the median time to onset of renal events was 104.5 days, and 6 of the 10 patients with renal adverse events reported resolution of 1 or more renal events; the median duration of events was 14 days.

Most events either had alternate pre--or post-renal etiologies, were confounded (eg, decreased renal function at baseline or occurred in context of disease progression), or were transient decreases in renal function that resolved spontaneously or had a negative dechallenge and/or rechallenge to sotorasib treatment.

In the integrated analysis of monotherapy data from patients treated at 960 mg QD, the incidence of renal events was lower than in CodeBreaK 200 (2.6% for sotorasib-treated patients in the integrated monotherapy population vs 5.9% for sotorasib-treated patients in CodeBreaK 200).

Overall, review of individual events did not find evidence of direct renal toxicity attributable to sotorasib.

6.1.10.4 Analysis of Select Adverse Events: Gastrointestinal Disorder Events

Adverse events in the system organ class of Gastrointestinal Disorders were the most frequently observed in CodeBreaK 200, including diarrhea, nausea, and vomiting, which are also known ADRs with sotorasib. In CodeBreaK 200, 118 patients (69.8%) in the

sotorasib group and 88 patients (58.3%) in the docetaxel group had a gastrointestinal adverse event, and the most commonly reported (sotorasib, docetaxel) gastrointestinal adverse events were diarrhea (41.4%, 25.8%), nausea (26.0%, 24.5%), constipation (13.0%, 19.2%), vomiting (13.0%, 9.9%), abdominal pain (11.8%, 6.0%), and stomatitis (1.8%, 12.6%). Grade 3 or higher gastrointestinal adverse events were reported for 35 patients (20.7%) in the sotorasib group and 11 patients (7.3%) in the docetaxel group, and the most common (sotorasib, docetaxel) grade 3 or higher gastrointestinal adverse events were diarrhea (13.6%, 2.6%), abdominal pain (3.0%, 1.3%), and nausea (2.4%, 0.7%). Serious gastrointestinal adverse events were reported in 14 patients (8.3%) in the sotorasib group and 9 patients (6.0%) in the docetaxel group, including diarrhea (3.0%, 1.3%), abdominal pain (1.8%, 0.7%), and nausea (1.2%, 0.7%).

The gastrointestinal disorder events were managed through dose holds and/or reductions and supportive care (eg, antidiarrheals, antiemetics) and rarely led to permanent discontinuation of sotorasib or docetaxel: dose interruption and/or reduction in 43 patients (25.4%) in the sotorasib group and 11 patients (7.3%) in the docetaxel group and discontinuation of investigational product in 2 patients (1.2%) in the sotorasib group (diarrhea and pancreatitis) and 2 patients (1.3%) in the docetaxel group (nausea, stomatitis, and vomiting).

The results from CodeBreaK 200 were consistent with results from an integrated analysis of patients with NSCLC treated at 960 mg QD, where gastrointestinal disorders adverse events were reported for 377 patients (68.7%) and the most frequently reported gastrointestinal adverse events were diarrhea (41.0%), nausea (25.7%), vomiting (14.9%), constipation (14.4%), and abdominal pain (10.2%).

6.1.10.4.1 Diarrhea

A total of 70 out of 169 sotorasib-treated patients had diarrhea in CodeBreaK 200: 29 patients (17.2%) had grade 1 diarrhea, 18 patients (10.6%) had grade 2 diarrhea, 23 patients (13.6%) had grade 3 diarrhea. There were no grade 4 or fatal diarrhea events in the sotorasib group. A total of 5 sotorasib-treated patients had serious adverse events of diarrhea requiring hospitalization. Of these, 2 patients had sequelae including potassium imbalance, dehydration, and renal changes. Both events of diarrhea were treated and the event resolved. One patient did not resume sotorasib treatment, while sotorasib treatment was resumed at a lower dose for the second patient with no progression. The other 3 patients had diarrhea events without sequelae. The diarrhea events were also confounded by other events (antibiotics for urinary tract

infection, pembrolizumab-related diarrhea) and an alternate etiology of colitis confirmed by a CT scan.

For the events of diarrhea, the median time to onset was 47.5 days, and 91.4% of patients reported resolution of 1 or more events. Diarrhea was managed by dose interruption in 26 patients (15.4%) and dose reduction in 14 patients (8.3%). The median duration of diarrhea per patient was 22 days and the median duration of treatment interruptions was 9 days. Of the 70 patients who had diarrhea, 53 patients (75.7%) took an antidiarrheal medication.

6.1.11 Laboratory Assessments and Vital Signs

There were no notable trends in laboratory values, vital signs, physical findings, or other observations related to safety, and the results were consistent with the known safety profile of sotorasib. There were no patterns or trends for increases in renal-related laboratory assessments (creatinine, albumin, and urine protein increase). Increased ALT and increased AST are known ADRs for sotorasib. In CodeBreaK 200 increases in ALT, AST, total bilirubin, and alkaline phosphatase were consistent with those previously observed in the sotorasib clinical development program and described in the prescribing information. A summary of worst clinical chemistry laboratory toxicity changes from baseline in liver laboratory values is shown in Table 28.

6.1.12 Patient-reported Outcomes

The exploratory analysis of GP5 of FACT-G showed patients receiving docetaxel were more severely bothered by their side effects compared with patients receiving sotorasib (odds ratio = 5.71, 95% CI: 2.98, 10.91) (Figure 18 and Figure 20 in Appendix 4).

Based on PRO-CTCAE, patients treated with docetaxel had symptoms at a higher severity (pain: odds ratio = 2.94, 95% CI: 1.24, 6.96; aching muscles: odds ratio = 4.40, 95% CI: 1.56, 12.43; aching joints: odds ratio = 4.17, 95% CI: 1.43, 12.20; mouth; throat sores: odds ratio = 4.26, 95% CI: 1.59, 11.47) (Figure 20 in Appendix 4).

Furthermore, their symptoms more strongly interfered with their usual or daily activities (pain: odds ratio = 3.18, 95% CI: 1.22, 8.34); aching muscles: odds ratio = 3.90, 95% CI: 1.12,13.58; aching joints: odds ratio = 10.68, 95% CI: 3.42, 33.35) (Figure 20 in Appendix 4).

Results from the EORTC QLQ-LC13 questionnaire also showed that patients treated with docetaxel had symptoms at a higher severity: dyspnea (odds ratio = 43.58, 95% CI: 1.98, 6.46), haemoptysis (odds ratio = 12.63, 95% CI: 2.35, 68.0), sore mouth

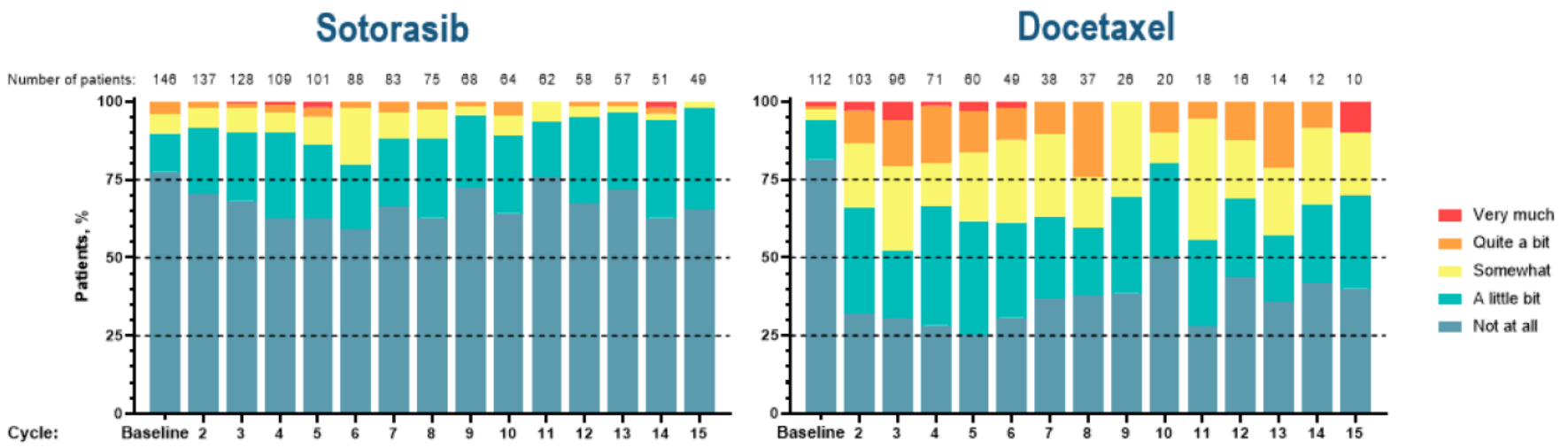
(odds ratio = 3.62, 95% CI: 1.54, 8.53), dysphagia (odds ratio = 1.77, 95% CI: 0.80, 3.95), peripheral neuropathy (odds ratio = 2.25, 95% CI: 1.14, 4.43), alopecia (odds ratio = 53.59, 95% CI: 24.85, 115.56, pain in arm or shoulder (odds ratio = 1.06, 95% CI: 0.55, 2.07) and pain in other parts (odds ratio = 1.77, 95% CI: 0.91, 3.34) (Figure 21 in Appendix 4).

As discussed in Section 6.1.10.4, diarrhea is a common adverse event for patients receiving sotorasib and is managed by dose modifications and anti-diarrheal medication. As part of the EORTC QLQ-C30 questionnaire, patients provided PRO data on assessment of symptom scales over time, including assessment of their diarrhea symptoms. The results, show that by 12 weeks postdose, most patients in both the sotorasib and docetaxel groups felt that they had diarrhea “not at all” (64 of 106 responding patients [60.4%] in the sotorasib group and 52 of 69 responding patients [75.4%] in the docetaxel group; odds ratio [based on generalized estimating equation at week 12] = 0.38; 95% CI: 0.20, 0.74).

Results from other symptoms assessed by the EORTC QLQ-C30 questionnaire are displayed in Figure 22 in Appendix 4.

Completion rates for GP5/FACT-G and for PRO-CTCAE in the sotorasib group were 89.5% and 90.1%, respectively at baseline. In the docetaxel group the corresponding values at baseline were 76.4% and 77.0%. Compliance rates for GP5 and PRO-CTCAE at baseline were 90.0% to 90.6% for sotorasib and 83.6% to 84.3% for docetaxel. During follow-up, compliance rates increased compared to baseline and at week 12 were 95.9% for sotorasib and 95.5% for docetaxel. The corresponding completion rates, which decreased due to study drug discontinuation, were 62.0% and 39.7% at week 12.

Figure 18. FACT-G Analysis (Treatment Side-effects Bother) in CodeBreaK 200



FACT-G = Functional Assessment of Cancer Therapy Tool - General form
Data cutoff date: 02 August 2022
Source: Modified from Table 14-11-8-701 of CodeBreaK 200 Primary Analysis

6.1.13 Subgroup Analyses

In CodeBreaK 200, no meaningful differences were observed in the types of adverse events reported across subgroups of sex, race, age (intrinsic factors), or region (extrinsic factor). The incidence of adverse events tended to be numerically lower for men compared with women in most MedDRA system organ classes with notable exceptions of hepatobiliary disorders, investigations, and metabolism, and nutrition disorders system organ classes where the incidences of adverse events were similar for men and women. However, review of the events, including fatal adverse events, did not reveal any clinically meaningful differences between sexes.

6.1.14 Safety Results in Crossover Patients

As described in Section 5.1.3, 46 patients who were randomized to docetaxel crossed over to sotorasib treatment following centrally-confirmed progressive disease (referred to as “crossover patients”). The current status and clinical outcomes for these 46 crossover patients are described in Section 5.1.11.7. Among these patients the median duration of sotorasib treatment was 21 weeks administered over 7.0 cycles. The safety findings in these 46 patients were consistent with the overall study population treated with sotorasib. Of the 46 crossover patients, 43 (93.5%) had an adverse event, and the most common adverse events (occurring in ≥ 5 patients) were diarrhea (14 [30.4%] patients), dyspnea and nausea (7 [15.2%] patients each), COVID-19 and fatigue (6 [13.0%] patients each), and anemia, back pain, and decreased appetite (5 [10.9%] patients each].

A total of 11 (23.9%) patients had an adverse EOI. The types and frequency of adverse EOIs were consistent with the overall study population treated with sotorasib: 9 patients (19.6%) had hepatotoxicity adverse events (mostly laboratory value abnormalities), 1 patient (2.2%) had pneumonitis, and 1 (2.2%) had an adverse event of renal toxicity.

Of the 46 crossover patients, 15 (32.6%) had fatal adverse events. Consistent with the overall study population treated with sotorasib, most of these were due to disease progression. Other causes of fatal adverse events did not occur in more than 1 patient (2.2%) each.

6.2 CodeBreaK 100 Phase 2 part B

6.2.1 Exposure to Sotorasib

As of 18 January 2023, the median (min, max) duration of treatment was 4.21 (0.0, 18.7) months for the 960 mg group and 4.02 (0.4, 16.9) months for the 240 mg

group. The (median [min, max]) cumulative dose was 106 500.0 (960, 546 240.0) mg for the 960 mg group and 26 520.0 (2640, 123 120.0) mg for the 240 mg group.

6.2.2 Adverse Event Data Collection and Safety Analyses

Per protocol, investigators were required to report all known signs and symptoms when an adverse event or serious adverse event was due to NSCLC, while deaths due to disease progression in the absence of signs and symptoms were required to be reported as the primary tumor type. Consistent with the analyses performed for CodeBreaK 200, and to allow for a more clinically relevant description of safety, a list of select preferred terms within the neoplasms system organ class reflective of the primary tumor and representing disease progression events were excluded from all safety analyses. These terms are listed in Table 36 in Appendix 6.

6.2.3 Overall Adverse Events

As of 18 January 2023, adverse events were reported for 101 patients (97.1%) in the 960 mg sotorasib group and 96 patients (92.3%) in the 240 mg sotorasib group (Table 29). The most common adverse events (≥ 15% of patients in either group [960 mg, 240 mg]) were diarrhea (39.4%, 31.7%), nausea (23.1%, 19.2%), increased ALT (14.4%, 17.3%), decreased appetite (17.3%, 10.6%), fatigue (15.4%, 12.5%), and vomiting (15.4%, 9.6%).

Adverse events that occurred more frequently (≥ 5% difference) in the 960 mg group compared with the 240 mg group were diarrhea, vomiting, decreased appetite, hypokalemia, and back pain. Treatment-related adverse events were reported for 86 patients (82.7%) in the 960 mg group and 64 patients (61.5%) in the 240 mg group (Table 29).

Table 29. Summary of Treatment-emergent Adverse Events (CodeBreaK 100 Phase 2 Part B NSCLC - Safety Analysis Set)

	Sotorasib 240 mg (N = 104) n (%)	Sotorasib 960 mg (N = 104) n (%)
All treatment-emergent adverse events	96 (92.3)	101 (97.1)
Grade ≥ 3	51 (49.0)	64 (61.5)
Grade ≥ 4	6 (5.8)	16 (15.4)
Serious adverse events	34 (32.7)	38 (36.5)
Leading to discontinuation of sotorasib	13 (12.5)	17 (16.3)
Leading to dose reduction/interruption of sotorasib	41 (39.4)	49 (47.1)
Fatal adverse events	4 (3.8)	6 (5.8)
Treatment-related treatment-emergent adverse events	64 (61.5)	86 (82.7)
Grade ≥ 3	20 (19.2)	37 (35.6)
Grade ≥ 4	1 (1.0)	7 (6.7)
Serious adverse events	8 (7.7)	14 (13.5)
Leading to discontinuation of sotorasib	10 (9.6)	13 (12.5)
Leading to dose reduction/interruption of sotorasib	23 (22.1)	41 (39.4)
Fatal adverse events	0 (0.0)	1 (1.0)

eCRF = electronic case report form; N = Number of patients in the analysis set; n = Number of patients with observed data.
A treatment-related adverse event was any treatment-emergent adverse event with the relationship flag on the Events eCRF indicating there was a reasonable possibility that the event may have been caused by investigational medicinal product. In the unlikely event that the relationship was missing, the treatment-emergent event was considered treatment-related.
Grade 5 fatal adverse events may have staredt prior to data cutoff and result in death after cutoff. These events were summarized with grade 5, but the death after data cutoff were not included in analysis.
Coded using Medical Dictionary for Reulatory Activites, version 25.1. Graded using Comon Terminolog Criteria for Adverse Events, version 5.0 criteria.
The following preferred terms were excluded as they represent disease progression events: Disease progression, Non-small cell lung cancer, Non-small cell lung cancer metastatic, Lung adenocarcinoma, Metastases to central nervous system, Lung neoplasm, Lung neoplasm malignant, Lymphangiosis carcinomatosa, Malignant neoplasm progression, Metastases to meninges.
Data cut-off date 18JAN2023
Source: Table 14-6.1-501 of Study 20170543 Phase 2 part B 90-day Safety Update

6.2.4 Serious Adverse Events

Serious adverse events were reported for 38 patients (36.5%) in the 960 mg group and 34 patients (32.7%) in the 240 mg group (Table 29). The most frequently reported serious adverse events (reported in ≥ 2% of patients in either group [960, 240 mg]) were pneumonia (1.0%, 4.8%), and drug-induced liver injury (2.9%, 1.0%).

Serious treatment-related adverse events were reported for 14 patients (13.5%) in the 960 mg group and 8 patients (7.7%) in the 240 mg group (Table 29). The most frequently reported serious treatment-related adverse event (reported in ≥ 2% of patients in either group [960 mg, 240 mg) was drug induced liver injury (2.9%, 1.0%).

6.2.5 Grade ≥ 3 Adverse Events

As of 18 January 2023, grade ≥ 3 adverse events generally occurred at a lower frequency in the 240 mg dose group compared with the 960 mg dose group.

Overall, 64 patients (61.5%) in the 960 mg group and 51 patients (49.0%) in the 240 mg group had grade ≥ 3 adverse events (Table 29). The most common grade ≥ 3 adverse events (≥ 3% of patients in either group [960, 240 mg]) were diarrhea (9.6%, 4.8%), increased ALT (8.7%, 6.7%), increased AST (5.8%, 2.9%), pneumonia (1.0%, 5.8%) increased gamma-glutamyltransferase (3.8%, 1.9%), vomiting (3.8%, 1.0%), dyspnea (3.8%, 1.9%), and hypokalemia (3.8%, 0.0%).

Grade ≥ 3 adverse events that occurred more frequently (≥ 2% difference) in the 960 mg group compared with the 240 mg group were diarrhea, increased ALT, increased AST, vomiting, and hypokalemia. The only grade ≥ 3 adverse event that occurred more frequently (≥ 2% difference) in the 240 mg group compared with the 960 mg group was pneumonia.

Grade ≥ 3 treatment-related adverse events were reported for 37 patients (35.6%) in the 960 mg group and 20 patients (19.2%) in the 240 mg group (Table 29).

6.2.6 Fatal Adverse Events

As of 18 January 2023, fatal adverse events were reported for 6 patients (5.8%) in the 960 mg group and 4 patients (3.8%) in the 240 mg group (Table 29). The most frequently reported fatal adverse event (> 1 patient in either group [960, 240 mg]) was pneumonia (0.0%, 1.9%). One treatment-related fatal adverse event of preferred term ‘death’ was reported in the 960 mg group. The patient had stable disease at baseline and died at home from an unknown cause on study day 3; no autopsy was performed and the investigator assessed the death as related to sotorasib due to lack of alternate etiology. No treatment-related fatal adverse events were reported in the 240 mg group. Review of the fatal adverse events did not identify any notable trends or patterns.

6.2.7 Adverse Events Leading to Dose Reduction/Interruption or Discontinuation of Sotorasib

Dose Reduction or Interruption

As of 18 January 2023, adverse events leading to interruption or dose reduction of sotorasib were reported in 49 patients (47.1%) in the 960 mg group and 41 patients (39.4%) in the 240 mg group (dose interruption) (Table 29). The most frequently reported adverse events leading to dose modification of sotorasib (reported in ≥ 2% of

patients [960, 240 mg]) were diarrhea (18.3%, 7.7%), increased ALT (5.8%, 8.7%), increased AST (3.8%, 5.8%), nausea (3.8%, 1.9%), increased blood alkaline phosphatase (1.9%, 3.8%), hepatotoxicity (2.9%, 1.9%), pneumonia (0.0%, 2.9%), and hepatitis (3.8%, 0.0%). Of note, dose reductions were not permitted for patients in the 240 mg group.

Forty-one patients (39.4%) in the 960 mg group and 23 patients (22.1%) in the 240 mg group had treatment-related adverse events leading to sotorasib treatment interruption or dose reduction (Table 29).

Treatment Discontinuation

In CodeBreaK 100 phase 2 Part B dose comparison, adverse events leading to sotorasib treatment discontinuation were reported for 17 patients (16.3%) in the 960 mg group and 13 patients (12.5%) in the 240 mg group (Table 29). The most common adverse event that led to sotorasib discontinuation (≥ 2% of patients in either group [960, 240 mg]) was pneumonitis (2.9%, 0.0%).

Thirteen patients (12.5%) in the 960 mg and 10 patients (9.6%) in the 240 mg group had treatment-related adverse events leading to sotorasib treatment discontinuation (Table 29). The most common treatment-related adverse event that led to sotorasib discontinuation (≥ 2% of patients in either group [960, 240 mg]) was pneumonitis (2.9%, 0.0%).

6.2.8 Adverse Events of Interest

Hepatotoxicity, renal toxicity, and pneumonitis were prespecified as adverse EOIs.

6.2.8.1 Hepatotoxicity

As of 18 January 2023, in CodeBreaK 100 phase 2 Part B dose comparison, the overall patient incidence of hepatotoxicity adverse events (33 patients [31.7%] in the 960 mg group vs 27 patients [26.0%] in the 240 mg group) and grade ≥ 3 events (20 patients [19.2%] in the 960 mg group vs 16 patients [15.4%] in the 240 mg group) were lower in the 240 mg group than the 960 mg group.

6.2.8.2 Renal Toxicity

Renal toxicity (narrow search) adverse events of interest were reported for 2 patients (1.9%) in the 960 mg group with preferred terms of acute kidney injury and renal failure. In 1 of these patients, acute kidney injury was identified via cycle 1, day 1 predose labs and the event subsequently resolved during sotorasib treatment. In the other patient,

renal failure occurred in the context of disease progression and hypoxemia. No renal toxicity adverse events of interest were grade ≥ 3 or led to sotorasib discontinuation or modification. No renal toxicity (narrow search) adverse events of interest were reported for patients in the 240 mg dose group.

6.2.8.3 Pneumonitis

As of 18 January 2023, in CodeBreaK 100 phase 2 Part B, the incidence of ILD/pneumonitis was lower in patients in the 240 mg group than in patients in the 960 mg group (4 patients [3.8%] in the 960 mg group and 1 patient [1.0%] in the 240 mg group).

6.2.9 Analysis of Adverse Events by Organ System or Syndrome

Adverse events in the system organ class of Gastrointestinal Disorders were the most frequently observed in CodeBreaK 100 phase 2 Part B. Diarrhea, nausea, and vomiting were the most common gastrointestinal disorders events reported. These events were managed through dose holds and/or reductions and supportive care (eg, antidiarrheals, antiemetics) and rarely led to permanent discontinuation of sotorasib. As of 18 January 2023, in CodeBreaK 100 phase 2 Part B, the incidence of gastrointestinal disorder adverse events, including the most common gastrointestinal events of diarrhea, nausea, and vomiting and ≥ grade 3 gastrointestinal events, was lower in the 240 mg group than the 960 mg group. Specifically, in the 960 mg group, 60.6% of patients had a gastrointestinal disorder adverse event of any grade, 18.3% had grade ≥ 3, and 4.8% had serious adverse events. Twenty-five patients (24.0%) had dose modifications and 1 patient (1.0%) discontinued sotorasib due to a gastrointestinal disorder adverse event. In the 240 mg group, 55.8% of patients had a gastrointestinal disorder adverse event of any grade, 8.7% had grade ≥ 3, and 5.8% had serious events. Thirteen patients (12.5%) had dose modifications and no patients discontinued sotorasib due to a gastrointestinal disorder adverse event.

6.2.10 Laboratory Assessments and Vital Signs

There were no notable trends in laboratory values, vital signs, physical findings, and other observations related to safety, and the results were consistent with the known safety profile of sotorasib. Increased ALT and increased AST are known ADRs for sotorasib. In CodeBreaK 100 phase 2 Part B, increases in ALT, AST, total bilirubin, and ALP were consistent with those previously observed in the sotorasib program and described in the prescribing information. There were no confirmed Hy's law cases.

Shifts in ALT, AST, total bilirubin, and ALP were similar between dose groups, though there were more grade 4 ALT and AST elevations among patients in the 960 mg group than among patients in the 240 mg group. All grade 4 ALT/AST elevations resolved with dose hold/reduction or discontinuation and treatment with corticosteroids (hepatoxicity events and the effect of prior checkpoint inhibitor therapy is discussed in Section 6.1.10.1)

6.3 Long-term Safety

No significant safety findings have been identified from long-term follow-up in clinical studies conducted with sotorasib.

6.4 Adverse Drug Reactions

Adverse events in the 923 patients with any tumor type who were treated with sotorasib monotherapy at any dose included in the sNDA submission were evaluated to identify additional ADRs. These patients were from the integrated analysis of pooled monotherapy data (960 mg monotherapy groups and the total monotherapy population) (defined under the main Section 6 heading). The identified ADRs are diarrhea, nausea, vomiting, abdominal pain (includes abdominal pain, abdominal pain upper, abdominal pain lower), fatigue, AST increased, ALT increased, bilirubin increased (includes bilirubin increased and hyperbilirubinaemia), alkaline phosphatase increased, decreased appetite, and ILD/pneumonitis.

6.5 Pharmacovigilance and Risk Management

Routine pharmacovigilance and risk minimization activities (ie, risk communications through prescribing information, labeling, and packaging) are considered sufficient to manage the risks associated with the use of sotorasib. The cumulative estimated postmarketing exposure from launch through 27 May 2023 is 5444 patient-years. Evaluation of the postmarketing safety data has not resulted in the detection of any new risks for sotorasib. Summarized below are available post marketing data for the key risks of hepatotoxicity, ILD and diarrhea. Limitations of post-marketing safety reports should be considered when interpreting these results, including the voluntary nature of adverse event reporting, the increased likelihood of reporting of more serious vs less serious adverse events, incomplete details in post-marketing reports making causal associations between drug exposure and adverse events difficult to assess.

Hepatic events: cumulatively a total of 812 events (15 per 100 patient-years) were reported from all sources to include regulatory authorities, literature, postmarking

non-interventional studies, and solicited sources using the drug related hepatic disorders standardized MedDRA query (SMQ) (broad scope). Of these, 360 were serious. The most commonly reported preferred terms (n > 50) were hepatotoxicity (n = 107), ALT increased (n = 72), hepatic enzyme increased (n = 72), hepatic function abnormal (n = 69), AST increased (n = 62), hepatic cytolysis (n = 62), liver function test increased (n = 58), and liver disorder (n = 55). Three fatal events, hepatotoxicity (n = 2) and hepatitis (n = 1), were reported. These cases did not contain sufficient information for causal assessment.

Interstitial Lung Disease (ILD): cumulatively, 54 events (1 per 100 patient-years) for the risk of ILD were reported from all sources to include regulatory authorities, literature, postmarking non-interventional studies, and solicited sources using the ILD SMQ (narrow Scope); of these 38 were serious**.** The reported preferred terms were pneumonitis (n = 26), ILD (n = 17), lung opacity (n = 5), pulmonary toxicity (n = 3), radiation pneumonitis (n = 2), and lung infiltration (n = 1). Four fatal events, pulmonary toxicity (n = 2), pneumonitis (n = 1), and ILD (n = 1), were reported. All fatal events were reported to have occurred in the context of either prior immunotherapy or prior radiotherapy.

Diarrhea: cumulatively, 491 events (9 per 100 patient years) for the risk of diarrhea were reported from all sources to include regulatory authorities, literature, postmarking non-interventional studies, and solicited sources using the diarrhea US FDA MedDRA Query (narrow Scope); 46 of which were serious. The reported preferred terms were diarrhea (n = 490) and diarrhea hemorrhagic (n = 1). There was 1 fatal case of diarrhea reported which contained insufficient information for a causal assessment.

Adverse event reports from the postmarketing safety data on the key sotorasib risks are consistent with the known safety profile, supporting the manageability of these risks in the real-world setting.

6.6 Overall Summary of Safety

- In CodeBreaK 200, after exclusion of disease progression events, the overall incidences of adverse events, including the combined incidence of grade 3 and 4 adverse events, serious adverse events, and incidence of treatment discontinuations due to adverse events were similar between sotorasib and docetaxel groups. When adjusted for exposure, patient incidence across all the safety summary categories were lower with sotorasib with the exception of adverse events leading to dose interruption.

- In CodeBreaK 200, overall deaths were primarily due to disease progression and were balanced between the sotorasib and docetaxel groups.
- Increases in liver enzymes associated with sotorasib have been effectively managed through treatment interruption, dose reductions, and use of steroids. There were no reports of severe sequalae of liver failure, or fatal events.
- Across the lung program, pneumonitis occurred rarely in patients treated with sotorasib. Pneumonitis events were effectively managed and mostly resolved with standard of care treatment. One event of fatal ILD was reported; however, the cause of death was recorded as disease progression.
- Gastrointestinal adverse events (diarrhea, nausea, vomiting) are common in patients receiving sotorasib. These events were managed through dose holds and/or reductions and supportive care (eg, antidiarrheals, antiemetics) and rarely led to permanent discontinuation of sotorasib.
- Data from CodeBreaK 100 are consistent with the safety profile of sotorasib observed in CodeBreaK 200, and support that sotorasib has a manageable safety profile at the 960 mg dose.
- The post marketing safety data are consistent with the known safety profile and cumulative experience of sotorasib.

7. Clinical Pharmacology

7.1 CodeBreaK 200

In CodeBreaK 200, following PO QD administration of 960 mg sotorasib, the geometric mean maximum plasma concentration (C_{max}) was 7040 and 6270 ng/mL on days 1 and 8, respectively. Geometric mean area under the concentration-time curve from 0 to 4 hours was 20 000 hr•ng/mL on day 1 and 17 300 hr•ng/mL on day 8. Differences in PK based on sex, race, disease status, body weight, and age, as well as mild renal or mild hepatic impairment were not clinically meaningful and were consistent with those observed in the 960 mg cohorts in the phase 1 and 2 portions of CodeBreaK 100. More advanced baseline disease burden, as defined by baseline tumor size and ECOG status, was independently associated with both higher sotorasib exposure and poorer clinical response. No significant positive exposure-response relationships for specific treatment-emergent adverse events of interest, including gastrointestinal disorders, diarrhea, ALT increase, AST increase, or hepatoxicity, were identified. Ability to assess exposure-response relationships was limited by the independent effects of baseline disease severity (quantified by baseline tumor size, ECOG status) on sotorasib exposure, efficacy, and safety.

7.2 CodeBreaK 100 Phase 2 Part B

For the dose comparison study (CodeBreaK 100 phase 2 Part B) sotorasib exposure, as assessed by C_{max} and area under the plasma concentration-time curve 0-24 hours, was 22% higher in the 960 vs the 240 mg group. Consistent with previous findings, more advanced baseline disease status was associated with both poorer clinical response and lower clearance resulting in higher sotorasib exposure. No significant exposure-safety relationships for treatment-emergent adverse events of interest including gastrointestinal disorders were identified. No correlation between sotorasib exposure and elevations of AST, ALT and total bilirubin was observed.

8. Benefits and Risks

8.1 Benefits

The key benefits of sotorasib are described below:

- Disease Progression and Death: Sotorasib lowered the risk of disease progression or death compared with docetaxel: The median PFS demonstrated a 34% reduction in the risk of progression or death for sotorasib compared with docetaxel. This benefit was consistent across all relevant subgroups, including history of CNS involvement and liver metastases at baseline. Overall survival was not different

between the 2 treatment groups suggesting that there is no survival detriment for patients treated with sotorasib.

- Durable Objective Response: Sotorasib monotherapy demonstrated a significant improvement in ORR in patients with previously treated *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC. Disease control rate was higher with sotorasib treatment compared with docetaxel and TTR for the patients treated with sotorasib was half of that observed for the patients treated with docetaxel. Median DOR was longer in the sotorasib group compared with the docetaxel group.
- Patient-reported Outcomes (Tolerability, Stabilized QoL, and Delayed Deterioration): There was a favorable change over time in global health status, physical functioning, and dyspnea with sotorasib treatment. Compared with docetaxel, sotorasib treatment delayed time to deterioration for global health status, physical functioning, dyspnea, and cough. Patients receiving docetaxel were more severely bothered by their side effects and experienced symptoms at a higher severity level and their symptoms more strongly interfered with their usual or daily activities than patients receiving sotorasib.
- Convenient and Flexible Oral Administration: Sotorasib can be administered orally (or via enteral feeding tube if needed), with or without food, in tablets or water dispersion, which provides patients with convenience and flexibility in their daily life. As of January 2023, availability of a 320 mg tablet strength reduces pill burden over the original 120 mg tablet strength.
- Sotorasib lengthened the median time to progression of CNS disease vs docetaxel among patients who had prior CNS disease
- A Predictive Biomarker to Identify Patient Population for Personalized Therapy: A predictive biomarker identified by a validated in vitro diagnostic test (tissue-based and plasma companion diagnostic are available in some countries) is used to select patients with *KRAS p.G12C* mutation who are most likely to benefit from sotorasib therapy and excludes those who would not benefit from treatment.

Overall, sotorasib monotherapy demonstrated improved PFS and rapid, durable responses, with a favorable effect on disease-related symptoms and physical function as assessed by PRO measures in patients with previously treated *KRAS p.G12C*-mutated locally advanced or metastatic NSCLC.

8.2 Risks

The following are the key risks of sotorasib treatment for the indication. These risks can be managed by monitoring, dose modification, temporary interruption until resolution or treatment discontinuation, and supportive care.

- Increased Liver Enzymes: Sotorasib has been associated with transient elevations of serum transaminases (ALT and AST), alkaline phosphatase, and bilirubin, which were mostly asymptomatic events in clinical studies. These elevations improved or resolved with interruption of treatment, dose reductions, and/or management with steroids, and there were no confirmed sequalae of liver failure, or fatal events.
- Pneumonitis/ILD: pneumonitis occurred rarely in patients treated with sotorasib who also had prior exposure to immunotherapy or radiotherapy. Pneumonitis events

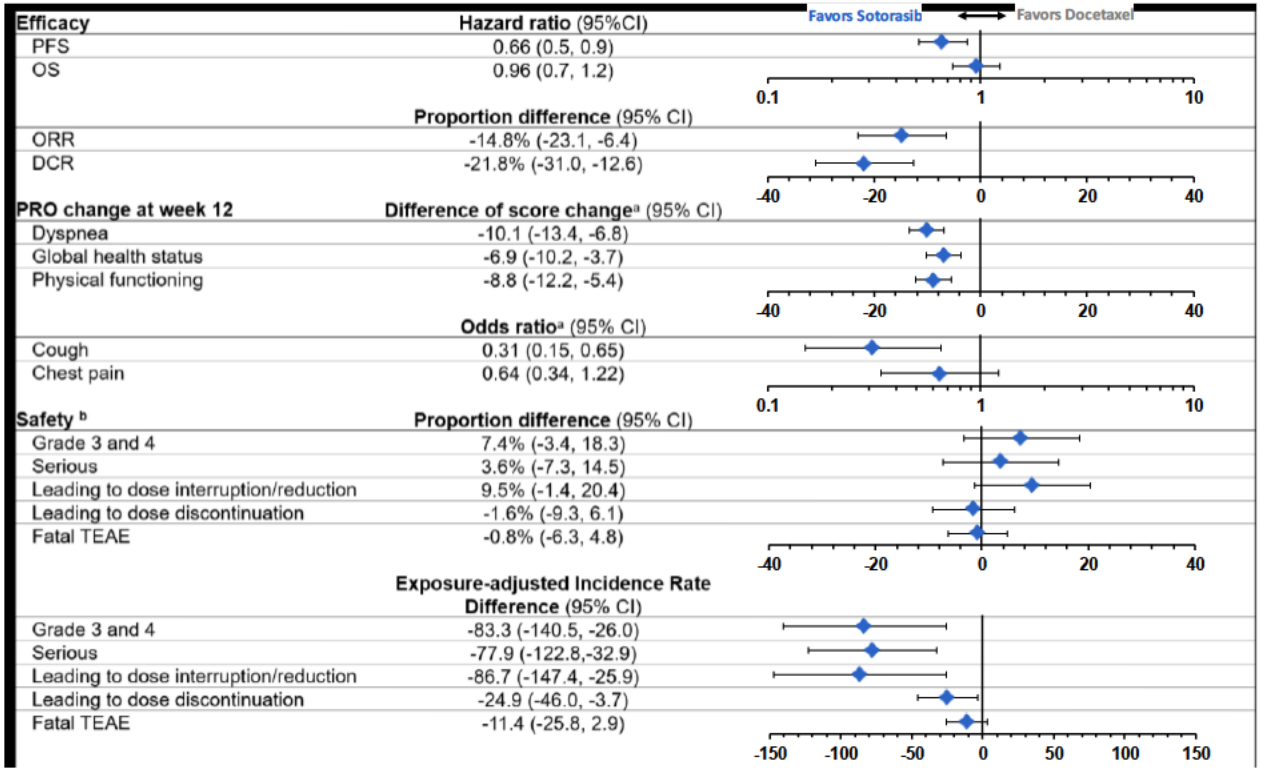
were effectively managed and mostly resolved with standard of care treatment. One event of fatal ILD was reported; however, the cause of death was recorded as disease progression.

- Diarrhea: diarrhea is a common adverse event, with an incidence of approximately 40% in patients treated with sotorasib. Most diarrhea events were grade 1 or 2, were managed with dose modifications and treatment interruptions and resolved with supportive care. Diarrhea rarely led to treatment discontinuations.

8.3 Benefit-Risk Conclusions

Sotorasib monotherapy demonstrated significant improvement in PFS and durable objective response, favorable effect on disease-related symptoms and physical function, with an acceptable and manageable safety profile. The consistent demonstration of benefit and no detrimental effect on OS therefore support a favorable benefit-risk assessment for 960 mg QD sotorasib. The benefits and risks of sotorasib are summarized in Figure 19.

Figure 19. Benefits and Risks of Sotorasib in Advanced/Metastatic NSCLC in CodeBreaK 200



DCR = disease control rate; NSCLC = non-smal cell lung cancer; ORR = overall objective response; OS = overall survival; PFS = progression free survival
02 August 2022[a] Difference was reversed and odds ratios inverted for consistent interpretation of forest plot direction (small value to the left favors sotorasib, large value to the right favor docetaxel).
[b] Excludesd disease-progression-related events in both groups. Exposure-adjusted incidence rate was per 100 patient-year.
Data cutoffs: 18 January 2023 for OS; 02 August 2022 for other endpoints
Source: PFS: Table 14-4.2.1 of CodeBreaK 200 Primary Analysis; ORR, DCR: Table 14-4.3.1 of CodeBreaK 200 Primary Analysis; OS: Table 14-4.5.1 of CodeBreaK 200 90-day Safety Update; Dyspnea/Global health status/physical status: Table 14-11-2-801 of CodeBreaK 200 Primary Analysis; Cough/chest pain: Table 14-11.3-801; Figure 90920230619-4.2.1; Figure 90920230619-4.2.1; Figure 90920230712-6.1.4 of CodeBreaK 200 Primary Analysis

9. Overall Conclusions

The data summarized in this briefing document demonstrate that oral sotorasib at a daily dose of 960 mg provides an important, safe, and effective treatment option for second-line therapy in patients with advanced NSCLC with *KRAS p.G12C* mutation, a disease area with serious unmet medical need.

The PFS results observed in CodeBreaK 200 represent a meaningful benefit for patients: more than twice as many patients in the sotorasib group were alive without progression at 1-year vs docetaxel, and meaningful benefit based on the PRO results were reported by patients receiving sotorasib vs docetaxel. The PFS benefit was robust: it was seen across all subgroups, the BICR-assessed PFS results and investigator-assessed results were consistent, and the observed PFS benefits were supported by prespecified and post hoc sensitivity analyses.

Other measures of effectiveness such as the increased tumor responses, faster TTR, and increased duration of those responses also favored sotorasib vs docetaxel, and support the PFS results. Further, the updated OS analysis at the 90-day safety update suggests no detrimental effect on survival for patients receiving sotorasib vs docetaxel.

The efficacy results observed in CodeBreaK 200 were supported by consistent results from CodeBreaK 100 phase 2 part A that supported the original marketing application, and from CodeBreaK 100 phase 2 part B that compared safety and efficacy of sotorasib at 2 doses. In CodeBreaK 100 phase 2 part A, the ORR was 36.3% (95% CI: 27.8, 45.4). In CodeBreaK 200 phase 2 part B, the ORR for patients who received 960 mg sotorasib, was 32.7% (95% CI: 23.8, 42.6). These results were consistent with the ORR in patients who received 960 mg in CodeBreaK 200 (28.1%; 95% CI: 21.5, 35.4), which was superior to the ORR seen with docetaxel in that study (13.2%; 95% CI: 8.6, 19.2).

Sotorasib has a manageable safety profile that is differentiated from docetaxel. Results from CodeBreaK 200 confirm that the targeted agent sotorasib is efficacious with a manageable adverse event profile (including key risks of elevated liver function enzymes, pneumonitis, and diarrhea). The benefit-risk assessment is enhanced by the fact that only patients who could possibly benefit (ie, those with a confirmed *KRAS p.G12C* mutation) would be treated with sotorasib. Risks associated with sotorasib use can be adequately managed through monitoring and dose modification guidance as described in the prescribing information.

The data supports a favorable benefit-risk assessment for 960 mg QD sotorasib with consistent demonstration of benefit observed across studies, endpoints, and prespecified subgroups and no detrimental effect on OS. A daily oral dose of 960 mg sotorasib provides an important treatment option for second-line therapy of *KRAS p.G12C* -mutated NSCLC, and fulfills an unmet need for this serious and life-threatening disease.

10. Literature References

American Association for Cancer Research (AACR) Project GENIE Consortium. AACR Project GENIE: Powering Precision Medicine through an International Consortium. *Cancer Discov*. 2017;7(8):818-831.

American Society of Clinical Oncology (ASCO). Systemic therapy for Stage IV non-small-cell lung cancer. https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/thoracic-cancer#/10201. Accessed 25 August 2019

Barbacid M. Ras genes. *Annu Rev Biochem*. 1987;56:779-827.

Barlesi F, Garon EB, Kim DW et al. Health-Related Quality of Life in KEYNOTE-010: a phase 2/III Study of Pembrolizumab Vs Docetaxel in Patients With Previously Treated Advanced, Programmed Death Ligand 1-Expressing NSCLC. *J Thorac Oncol*. 2019;14(5):793-801.

Biernacka A, Tsongalis PD, Peterson JD, et al. The potential utility of re-mining results of somatic mutation testing: KRAS status in lung adenocarcinoma. Cancer Genet. 2016;209(5):195-198.

Blackhall F, Kim DW, Besse B, et al. Patient-reported outcomes and quality of life in PROFILE 1007: a randomized trial of crizotinib compared with chemotherapy in previously treated patients with ALK-positive advanced non-small-cell lung cancer [published correction appears in J Thorac Oncol. 2015 Nov;10(11):1657]. J Thorac Oncol. 2014;9(11):1625-1633.

Bordoni R, Ciardiello F, von Pawel J, Cortinovis D, Karagiannis T et al. Patient-Reported Outcomes in OAK: A phase 3 Study of Atezolizumab Vs Docetaxel in Advanced Non-Small-cell Lung Cancer. *Clin Lung Cancer*. 2018;19(5):441-449

Borghaei H, Paz-Ares L, Horn L, et al Nivolumab vs docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627-1639.

Canon, J, Rex, K, Saiki, AY, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*. 2019;575;217-223

Charpidou A, Vathiotis I, Gkiozos I, et al. Exceptional antitumor responses beyond immune checkpoint inhibition in non-small cell lung cancer patients: insights into optimal therapy sequencing. J Thorac Dis. 2019;11(3):E25-E31

Cooley ME, Short TH, Moriarty HJ. Symptom prevalence, distress, and change over time in adults receiving treatment for lung cancer. *Psychooncology*. 2003;12(7):694-708

Cyramza® (ramucirumab) [prescribing information]. Indianapolis IN: Eli Lily and Company; June 2020.

Cui W, Franchini F, Alexander M, et al. Real world outcomes in KRAS G12C mutation positive non-small cell lung cancer. *Lung Cancer*. 2020;146:310-317.

de Langen AJ, Johnson ML, Mazieres J et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with $KRAS^{G12C}$ mutation: a randomised, open-label, phase 3 trial. Lancet. 2023 Mar 4;401(10378):733-746.

Dingemans AM C, Syrigos K, Livi L, et al. Intracranial efficacy of sotorasib vs docetaxel in pretreated *KRAS* G12C-mutated advanced non-small cell lung cancer (NSCLC): Practice-informing data from a global, phase 3, randomized, controlled trial (RCT). Journal of Clinical Oncology 2023 41:17_suppl, LBA9016-LBA9016

Engels FK, Verweij J. Docetaxel administration schedule: from fever to tears? A review of randomised studies. Eur J Cancer. 2005 May;41(8):1117-26.

Fernández-Medarde A, Santos E. Ras in cancer and developmental diseases. *Genes Cancer*. 2011;2(3):344-358.

Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN et al. Ramucirumab plus docetaxel vs placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014 Aug 23;384(9944):665-673.

Gandhi L, Rodríguez-Abreu D, Gadgeel S et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22):2078-2092.

Gralla RJ, Coon C, Taylor F et al. Evaluation of disease-related symptoms in patients with advanced squamous non-small cell lung cancer treated with nivolumab or docetaxel. *J Thorac Oncol*, 10 (Suppl 2) (2015), p. S233.

Gray JE, Hsu H, Younan D, Suri G, Chia V, Spira A, Johnson M. Real-world outcomes in patients with KRAS G12C-mutated advanced non-small cell lung cancer treated with docetaxel in second-line or beyond. Lung Cancer. 2023 Jul;181:107260.

Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019 Nov 21;381(21):2020-2031.

Hendriks LE, Kerr KM, Menis J, Mok TS, Nestle U, Passaro A, Peters S, Planchard D, Smit EF, Solomon BJ, Veronesi G, Reck M, on behalf of the ESMO Guidelines Committee, Non-oncogene addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology 2023. https://doi.org/10.1016/j.annonc.2022.12.013.

Hirth J, Watkins PB, Strawderman M, Schott A, Bruno R, Baker LH. The Effect of an Individual's Cytochrome CYP3A4 Activity on Docetaxel Clearance. *Clin Cancer Res.* 2000;6(4):1255-1258.

Hopwood P and Stephens R.J.Symptoms at presentation for treatment in patients with lung cancer: implications for the evaluation of palliative treatment. The Medical Research Council (MRC) Lung Cancer Working Party. *Br J Canc.* 1995; 71: 633-636

Jänne PA, van den Heuvel MM, Barlesi F, et al. Selumetinib Plus Docetaxel Compared With Docetaxel Alone and Progression-Free Survival in Patients With *KRAS*-Mutant Advanced Non-Small Cell Lung Cancer: The SELECT-1 Randomized Clinical Trial. *JAMA.* 2017;317(18):1844-1853

Jassem J, de Marinis F, Giaccone G, et al. Updated Overall Survival Analysis From IMpower110: Atezolizumab Vs Platinum-Based Chemotherapy in Treatment-Naive Programmed Death-Ligand 1-Selected NSCLC. J Thorac Oncol. 2021 Nov;16(11):1872-1882.

Jones RP, Sutton PA, Evans JP, et al. Specific mutations in KRAS codon 12 are associated with worse overall survival in patients with advanced and recurrent colorectal cancer. *Br J Cancer*. 2017;116(7):923-929.

Kenmotsu H, Tanigawara Y. Pharmacokinetics, dynamics and toxicity of docetaxel: Why the Japanese dose differs from the Western dose. Cancer Sci. 2015 May;106(5):497-

504. doi: 10.1111/cas.12647. Epub 2015 Mar 25. PMID: 25728850; PMCID: PMC4452149.

Ko YH, Lee MA, Hong YS, Lee KS, Park HJ, Yoo IeR, Kim YS, Kim YK, Jo KH, Wang YP, Lee KY, Kang JH. Docetaxel monotherapy as second-line treatment for pretreated advanced non-small cell lung cancer patients. Korean J Intern Med. 2007 Sep;22(3):178-185.

Krazati® prescribing information 2022, Mirati Therapeutics Inc. San Diego, California

Latimer, N., et al. (2014) Adjusting Survival Time Estimates to Account for Treatment Switching in Randomized Controlled Trials—an Economic Evaluation Context: Methods, Limitations, and Recommendations. Medical Decision Making 34(3):387-402

Lee, J.K., Sivakumar, S., Schrock, A.B. *et al.* 2022.Comprehensive pan-cancer genomic landscape of *KRAS* altered cancers and real-world outcomes in solid tumors. *Precis. Onc.* 6, 91

Liao YC, Liao WY, Shun SC, YU CJ, Yang PC, Lai YH. Symptoms, psychological distress, and supportive care needs in lung cancer patients. *Support Care Cancer*. 2011;19(11):1743-1751

Liu S-Y, Sun H, Zhou J-Y, et al. Clinical characteristics and prognostic value of the KRAS G12C mutation in Chinese non-small cell lung cancer patients. *Biomark Res*. 2020;8:22.

Lumakras® prescribing information 2023, Amgen, Thousand Oaks, California

McCormick F. K-Ras protein as a drug target. *J Mol Med* (Berl). 2016;94(3):253-258.

McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. Expert Rev Pharmacoecon Outcomes Res. 2011 Apr;11(2):163-169

Montero A, Fossella F, Hortobagyi G, Valero V. Docetaxel for treatment of solid tumours: a systematic review of clinical data. *Lancet Oncol.* 2005;6(4):229–239.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 1.2023. Accessed at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf on 18 January 2023

Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature.* 2013;503:548-551

Powell NR, Shugg T, Ly RC, Albany C, Radovich M, Schneider BP and Skaar TC. Life-Threatening Docetaxel Toxicity in a Patient With Reduced-Function CYP3A Variants: A Case Report. *Front. Oncol.* 2022;11:809527

Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. *Cancer Res.* 2012;72(10):2457-2467.

Reck M, Taylor F, Penrod JR, DeRosa M, Morrissey L, Dastani H, Orsini L, Gralla RJ. Impact of Nivolumab vs Docetaxel on Health-Related Quality of Life and Symptoms in Patients with Advanced Squamous Non-Small Cell Lung Cancer: Results from the CheckMate 017 Study. *J Thorac Oncol*. 2018;13(2):194-204.

Riely GJ, Kris MG, Rosenbaum D, Marks J, Li A, Chitale DA, Nafa K, Riedel ER, Hsu M, Pao W, Miller VA, Ladanyi M. Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma. Clin Cancer Res. 2008 Sep 15;14(18):5731-4. doi: 10.1158/1078-0432.CCR-08-0646. PMID: 18794081; PMCID: PMC2754127.

Robins, J. and A.Tsiatis. (1991). Correcting for Non-Compliance in Randomized Trials Using Rank Preserving Structural Failure Time Models. Communication in Statistics – Theory and Methods 20(8):2609-2631.

Robins, J. M. (1993). Information recovery and bias adjustment in proportional hazards regression analysis of randomized trials using surrogate markers. In Proceedings of the Biopharmaceutical Section, American Statistical Association, 24-33.

Siegel DA, Fedewa SA, Henley SJ, Pollack LA, Jemal A. Proportion of Never Smokers Among Men and Women With Lung Cancer in 7 US States. *JAMA Oncol.* 2021;7(2):302–304.

Silvestri G, Pritchard R, Welch HG. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: descriptive study based on scripted interviews. BMJ. 1998 Sep 19;317(7161):771-5. doi: 10.1136/bmj.317.7161.771. PMID: 9740561; PMCID: PMC28665.

Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. *Cell*. 2017;170:17-33.

Spira AI, Tu H, Aggarwal S, Hsu H, Carrigan G, Wang X, Ngarmchamnanrith G, Chia V, Gray JE. A retrospective observational study of the natural history of advanced non-small-cell lung cancer in patients with KRAS p.G12C mutated or wild-type disease. Lung Cancer. 2021;159:1-9.

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 17 Registries, Nov 2021 Sub (2000-2019) - Linked To County Attributes - Time Dependent (1990-2019) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2022, based on the November 2021 submission. Kaplan-Meier, Ederer II Method. Accessed 05 May 2022.

Takeda K, Negoro S, Tamura T, Nishiwaki Y, Kudoh S, Yokota S, Matsui K, Semba H, Nakagawa K, Takada Y, Ando M, Shibata T, Saijo N. Phase III trial of docetaxel plus gemcitabine versus docetaxel in second-line treatment for non-small-cell lung cancer: results of a Japan Clinical Oncology Group trial (JCOG0104). Ann Oncol. 2009. 20(5):835-841.

Taxotere® USPI, 2020 Sanofi-Aventis U.S. LLC, Bridgewater, NJ 08807; Taxotere® Summary of Product Characteristics, Sanofi Mature IP.

Tishelman C, Petersson LM, Degner LF, Sprangers MAG. Symptom prevalence, intensity, and distress in patients with inoperable lung cancer in relation to time of death. *J Clin Oncol*. 2007;25(34):5381-5389.

Tishelman C, Degner LF, Rudman A, et al. Symptoms in patients with lung carcinoma: distinguishing distress from intensity. *Cancer*. 2005;104(9):2013-2021.

United States Food and Drug Administration. A Series of Reports From the US FDA's Patient-Focused Drug Development Initiative. The Voice of the Patient: Lung Cancer. 2013. Available at https://www.fda.gov/media/130344/download. Accessed October 2020.

Werner JA, Davies R, Wahlstrom J, Dahal UP, Jiang M, et al. Mercapturate pathway metabolites of sotorasib, a covalent inhibitor of KRAS^{G12C}, are associated with renal toxicity in the Sprague Dawley rat. Toxicol Appl Pharmacol. 2021;423:115578.

World Health Organization. 2020 Statistics. Accessed April 2022. Available at https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf

11. Appendices

Appendix 1. Second-line Non-targeted Treatment Options for Non-small Cell Lung Cancer

Table 30. Second-line Non-targeted Treatment Options for Non-small Cell Lung Cancer

Product Name (INN)	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
Atezolizumab	injection (IV infusion): 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks	Study GO28915 (OAK) • median OS: 13.8 months • median PFS: 2.8 months • ORR: 14%	immune-related events (including pneumonitis, hepatitis, colitis, endocrinopathies); infusion related reactions, infections, and embryo-fetal toxicity
Docetaxel	Injection (IV infusion); 75 mg/m^2 every 3 weeks	Study TAX317 • median survival: 7.5 months • time to progression: 12.3 weeks • response rate: 5.5% Study TAX320 • median survival: 5.7 months • time to progression: 8.3 weeks • response rate: 5.7%	hematologic effects (including neutropenia, febrile neutropenia, anemia), infections, second primary malignancies, cutaneous reactions, neurologic reactions, eye disorders, asthenia, embryo-fetal toxicity, alcohol content, and tumor lysis syndrome
Nivolumab	injection (IV): 240 mg every 2 weeks or 480 mg every 4 weeks	Study CHECKMATE-017 (NCT01642004) • median OS: 9.2 months • ORR: 20% • median DOR: not reported median PFS: 3.5 months	immune-mediated reactions (including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and renal dysfunction, skin adverse reactions, and encephalitis), infusion related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity

Page 1 of 2

Footnotes are defined on the last page of the table

Table 30. Second-line Non-targeted Treatment Options for Non-small Cell Lung Cancer

Product Name (INN)	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
Pembrolizumab	injection (IV): 200 mg every 3 weeks or 400 mg every 6 weeks	Study KEYNOTE-010 (NCT01905657) vs docetaxel TPS ≥ 50% • median OS: 14.9 vs 8.2 months • median DOR: NR v 8.1 months • ORR: 30% vs 8% • median PFS: 5.2 vs 4.1 months TPS ≥ 1% • median OS: 10.4 vs 8.5 months • median DOR: NR vs 6.2 months • ORR: 18% vs 9% • median PFS: 3.9 vs 4.0	immune-mediated reactions (including pneumonitis, colitis, hepatitis, and hepatotoxicity, endocrinopathies, nephritis, skin adverse reactions, other adverse reactions), infusion related reactions, complications of allogeneic HSCT, and embryo-fetal toxicity
Pemetrexed	injection (IV): 500 mg/m^2 every 3 weeks	Study JMEI (NCT00004881) • median OS: 8.3 months • median PFS: 2.9 months • ORR: 8.5%	myelosuppression, renal failure, bullous, and exfoliative skin toxicity, interstitial pneumonitis, radiation recall, and embryo-fetal toxicity
Ramucirumab + Docetaxel	injection (IV): 10 mg/kg over 60 minutes on day 1 of a 21-day cycle prior to docetaxel infusion	Study REVEL (NCT01168973) vs placebo and docetaxel • median OS: 10.5 vs 9.1 months • median PFS: 4.5 vs 3.0 months • ORR: 22.9% vs 13.6%	hematologic effects, hemorrhage, gastrointestinal perforations, impaired wound healing, arterial thromboembolic events, hypertension, infusion-related reactions, worsening of pre-existing hepatic impairment, posterior reversible encephalopathy syndrome, proteinuria including nephrotic syndrome, thyroid dysfunction, and embryo-fetal risk

Footnotes are defined on the last page of the table Page 2 of 2

BID = twice daily; DOR = duration of response; HSCT = hematopoietic stem cell transplantation; INN = International Nonproprietary Name; IV = intravenous; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TPS = tumor proportion score

Source: Product prescribing information.

Appendix 2. Efficacy Endpoints and Statistical Methods for CodeBreaK 200

Table 31. Pre-Specified Efficacy Endpoints and Statistical Methods for CodeBreaK 200

Efficacy Endpoint	Definition	Primary Summary and Analysis Method
Primary		
PFS	Time from randomization until disease progression or death from any cause, whichever occurs first for all patients. Progression was based on BICR of disease response per RECIST v1.1	Distribution characterized based on Kaplan-Meier curves Inferential comparison between treatment groups used the log-rank test stratified by the randomization stratification factors. The hazard ratio and its 95% CI estimated using a Cox proportional hazards model stratified by the randomization stratification factors
Key Secondary		
OS	Time from randomization until death from any cause	Same as described for PFS
ORR	Proportion of patients with objective response (CR + PR), assessed by BICR per RECIST v1.1	The ORR calculated by treatment group and the associated 95% CI estimated using the Clopper-Pearson method The inferential comparison between treatment groups using the Cochran-Mantel-Haenszel Chi-square test controlling for the randomization stratification factors.
PROs as assessed by EORTC QLQ-LC13 and EORTC QLQ-C30	Change from baseline (cycle 1 day 1) to week 12 in disease-related symptoms of dyspnea composite (QLQ-C30 and QLQ-LC13); cough and chest pain (QLQ-LC13); and physical functioning and global health status (QLQ-C30)	The inferential comparison for change from baseline for dyspnea, physical functioning, and global health status through a MMRM. The inferential comparison for change from baseline for cough and chest pain through generalized estimating equations method.

Page 1 of 2

Footnotes are defined on the last page of the table.

Table 31. Pre-Specified Efficacy Endpoints and Statistical Methods for CodeBreaK 200

Efficacy Endpoint	Definition	Primary Summary and Analysis Method
Secondary		
DOR	Time from first evidence of PR or CR to disease progression or death due to any cause, whichever occurs first. Progression based on a BICR assessment of disease response per RECIST v1.1	Characterized using the Kaplan-Meier method based on the patients who achieve a best response of PR or better. No inferential comparison between treatment groups
DCR	Rate of confirmed objective response (CR or PR) + stable disease per RECIST v1.1 of at least 6 weeks measured	Summarized as for ORR
TTR	Time from randomization to first evidence of PR or CR	Summarized by the non-missing sample size (n), mean, standard deviation, median, minimum, and maximum for responders by study and regimen (side-by-side) using the full analysis set
Exploratory		
PFS2	Time from the date of randomization to second disease progression or disease progression on the next-line treatment (including crossover from docetaxel to sotorasib), or death from any cause, whichever occurs first for all patients	primarily analyzed using the same method as described for the PFS endpoints
Time to CNS progression	Time from randomization to disease progression/recurrence of CNS disease for the subset of patients with prior CNS disease at study entry	Kaplan-Meier estimate of CNS time to progression/recurrence for the subset of patients with prior CNS disease at study entry

Page 2 of 2

BICR = blinded independent central review; CNS = central nervous system; CR = complete response; DCR = disease control rate; DOR = duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of life Questionnaire Core 30; EORTC QLQ-LC13 = European Organization for Research and Treatment of Cancer Quality of life Questionnaire Lung Cancer 13; MMRM = mixed model for repeated measurements; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = progression-free survival after disease progression/disease progression on next line of treatment; PR = partial response; PRO = patient-reported outcome; QLQ-C30 = quality of life questionnaire 30-item core module; QLQ-LC13 = quality of life questionnaire lung cancer module; RECIST = response evaluation criteria in solid tumors; TTR = time to response
Source: Section 16.1.9 of of CodeBreaK 200 Primary Analysis

Appendix 3. Study Design and Efficacy Analysis Details: CodeBreaK 100 phase 2 Part B

Key Design Aspects

CodeBreaK 100 is an ongoing, phase 1/2, open-label, nonrandomized, study evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of sotorasib in patients with *KRAS p.G12C*-mutated NSCLC, CRC, and other solid tumors. Phase 1 was a first-in-human dose exploration/expansion portion of the study. The primary objectives of the phase-1 portion were to evaluate the safety and tolerability of sotorasib and to estimate the maximum tolerated dose (MTD) and/or a recommended dose (RP2D) of sotorasib in adult patients with *KRAS p.G12C*-mutated advanced solid tumors.

Phase 2 is a pivotal, open-label portion of the study designed to evaluate efficacy, safety/tolerability, and PK of sotorasib as monotherapy in patients with *KRAS p.G12C*-mutated advanced solid tumors (NSCLC, CRC, and other tumors). Phase 2 consisted of 2 parts. For Part A, the primary objective was to evaluate tumor ORR by RECIST v1.1 of 960 mg QD sotorasib (the RP2D declared from phase 1) as monotherapy in patients with *KRAS p.G12C*-mutated advanced solid tumors. The results from Part A demonstrated that sotorasib 960 mg QD was safe and effective under study conditions. However, sotorasib demonstrated a non-linear PK profile, with responses noted at all dose levels ranging from 180 to 960 mg. Upon review of the original marketing application, the US FDA requested a postmarketing requirement of a dose comparison study to evaluate a lower dose of sotorasib vs the 960 mg QD dose. This was communicated to global health authorities during the original application. Then, the protocol was amended and a dose of 240 mg QD was selected for further exploration in this dose comparison part of the study (phase 2 Part B) to investigate whether a lower dose can be as safe and efficacious as 960 mg QD.

For Part B, the primary objective was to evaluate tumor ORR assessed by RECIST v1.1 criteria of 960 mg QD sotorasib and 240 mg QD sotorasib as a monotherapy in patients with NSCLC.

The study consists of a screening period, a treatment period, a safety follow-up period, and long-term follow up period. This study enrolled 209 patients with previously treated locally advanced and unresectable or metastatic NSCLC with *KRAS p.G12C*. An independent DMC was convened for this study and reviewed safety and efficacy data per the DMC charter.

Tumor assessment was conducted by MRI and/or contrast enhanced CT and assessed per RECIST v1.1 by an independent radiologic laboratory. Daily treatment was to continue without interruption until disease progression, intolerance to treatment leading to treatment discontinuation, initiation of another anticancer therapy, or withdrawal of consent, whichever occurred first. Tumor assessment and response was confirmed by central review.

Safety was monitored by assessing serious and nonserious adverse events, safety laboratory tests, vital signs, and electrocardiograms. Adverse events were graded according to the National Cancer Institute CTCAE, version 5.0. The PRO/QOL assessments included QLQ-C30, QLQ-LC13, NSCLC System Assessment Questionnaire [SAQ], PGIC and PGIS in cough, dyspnea, and chest pain, select questions from the PRO-CTCAE, and a single item about symptom bother (GP5 of FACT-G).

Eligible patients were men or women ≥ 18 years of age, with *KRAS p.G12C*-mutated advanced NSCLC, as assessed by molecular testing. Patients were randomized in a 1:1 allocation ratio to either sotorasib 960 mg QD or sotorasib 240 mg QD in an open label manner. Randomization was stratified by the number of prior lines of therapy in advanced disease (1 and 2 vs > 2), history of CNS involvement (yes vs no), race (Asian vs non-Asian), and ECOG (< 2 vs 2). This patient population was similar to the CodeBreaK 200 patient population.

Health authority input regarding the design of CodeBreaK 100 was received through formal interactions in the United States, European Union, and other regions in 2019 through 2021. In 2021, during the review of the original marketing application, feedback from US FDA led to substantial changes to the study design.

The key changes made to the CodeBreaK 100 protocol included the addition of phase 2 Part A (expansion) with Amendment 2 and the addition of phase 2 Part B (dose comparison) with Amendment 7. The protocol for Study 20170543 (originally dated 14 May 2018) was amended 10 times as of the date of this briefing document.

Statistical Methodology: Sample Size and Planned Analyses

Approximately 200 patients with NSCLC were to be enrolled and randomly assigned in a 1:1 ratio to receive sotorasib 960 or 240 mg QD. The sample size was chosen to provide the point estimate of ORR difference between 2 treatment groups with acceptable precision based on its confidence interval. With a sample size of 200, when at least 11% ORR difference is observed between the 2 treatment groups, the lower bound of its 2-sided 90% CI would be able to exclude zero if assuming the ORR in the 960 mg treatment group was 35%.

An interim data review team (DRT) analysis was planned when approximately 40% of patients had the opportunity for at least 4 months of follow-up. At this interim analysis, aggregate safety data from all enrolled patients and the ORR based on data from patients who had ≥ 4 months follow-up were summarized and reviewed by the DRT. With 80 patients, the minimal observed ORR difference would be 16% for the lower bound of its 2-sided 90% CI to exclude 0, assuming the ORR in the 960 mg group is 35%. There were no formal stopping guidelines at this interim analysis. The data were not locked at this interim analysis.

The primary analysis was planned approximately 6 months after the last patient enrolled in phase 2 Part B. All safety, efficacy, laboratory, and PK data were summarized. Additional analyses after the primary analysis were conducted to update the DOR and OS. The final analysis will occur at the end of study (defined as last patient last visit).

Analysis of Endpoints

A summary of statistical methods for analysis of efficacy endpoints in the phase 2 Part B portion of CodeBreaK 100 are presented in Table 32. The analyses of the efficacy endpoints were conducted on the full analysis set.

Table 32. Efficacy Endpoints and Statistical Methods for CodeBreaK 100 Phase 2 Part B

Efficacy Endpoint	Definition	Primary Summary and Analysis Method
Primary		
ORR	Proportion of patients with a best overall response of confirmed CR or confirmed PR, measured by CT or MRI, and assessed per RECIST v1.1 by BICR. CR and PR required confirmatory CT or MRI repeat assessment at least 4 weeks after the first detection of response.	The number and percentage of patients with a best overall response of CR, PR, stable disease, progressive disease, not evaluable was provided. ORR was summarized with Clopper-Pearson exact 95% CI. Patients without a post-baseline tumor assessment were considered nonresponders
Secondary		
PFS	Time from the date of the first dose of sotorasib to the date of disease progression or death due to any cause, whichever occurs first, as assessed per RECIST v1.1 by BICR	Summarized with Kaplan-Meier curves, median, quartiles, and rates for selected timepoints (eg, 6 and 12 months).
OS	Time from the date of the first dose of sotorasib until the date of death from any cause	Summarized with Kaplan-Meier curves, median, quartiles, and rates for selected timepoints (eg, 6 and 12 months).
DOR	Time from first PR or CR to disease progression per RECIST v1.1 or death, whichever occurs first. The DOR was calculated only for patients who achieved a confirmed best overall response of PR or CR per RECIST v1.1	Summarized with Kaplan-Meier median, quartiles and rates for select durations (eg, > 3, > 6, > 9, > 12 months)
DCR	Proportion of patients whose best overall response was CR, PR, or stable disease > 5 weeks	Summarized as for ORR
TTR	Time from the date of the first dose of sotorasib to the date of the first PR or CR. The TTR was calculated only for patients who achieved a confirmed best overall response of PR or CR per RECIST v1.1	Summarized by the nonmissing sample size (n), mean, standard deviation, median, minimum, and maximum for responders

Page 1 of 2

Footnotes are defined on the last page of the table.

Table 32. Efficacy Endpoints and Statistical Methods for CodeBreaK 100 Phase 2 Part B

Efficacy Endpoint	Definition	Primary Summary and Analysis Method
Secondary, continued		
PRO	Changes in cancer-specific symptoms and overall health status using PRO instruments: EORTC QLQ-C30 + disease-specific modules QLQ-LC13 and NSCLC SAQ for NSCLC; PGIS and PGIC in cough, dyspnea, and chest pain among patients with NSCLC; selected questions from the PRO-CTCAE library; a single item about symptom bother (GP5) of the FACT-G	Descriptive summary across visits. MMRM model to describe change from baseline over time in EORTC QLQ-C30 (dyspnea, physical functioning, global health status) and EORTC QLQ-LC13 (dyspnea, cough, chest pain)

Page 2 of 2

BICR = blinded independent central review; CR = complete response; CT = computed tomography; DCR = disease control rate; DOR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy Tool - General form; MMRM = mixed model for repeated measurements; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PGIC = patient global impression of change; PGIS = patient global impression of severity; PR = partial response; PRO-CTCAE = patient-reported outcome version of the Common Terminology Criteria for Adverse Events; QLQ-C30 = quality of life questionnaire 30-item core module; QLQ-LC13 = quality of life questionnaire lung cancer module; RECIST = Response Evaluation Criteria in Solid Tumors; SAQ = symptom assessment questionnaire; TTR = time to response

Source: Section 7.1 and Section 16.1.9 of 20170543 phase 2 Part B CSR

Appendix 4. CodeBreaK 200 Patient-reported Outcomes

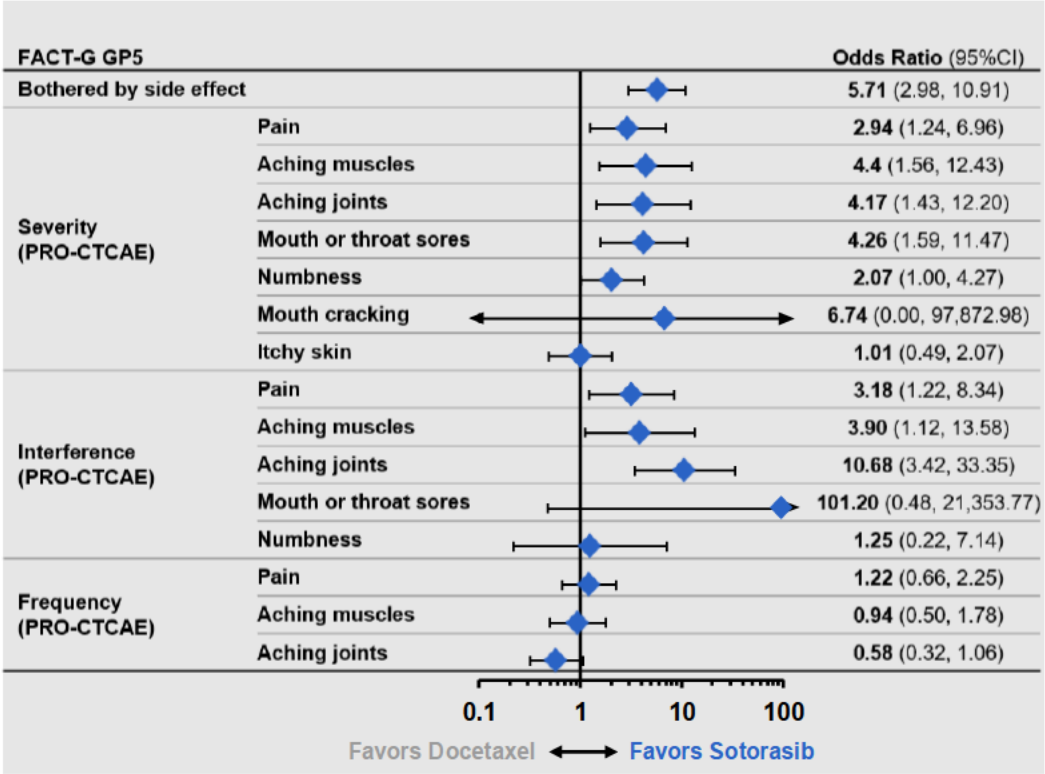
Table 33. Thresholds to Determine Clinically Meaningful Deterioration or Clinically Meaningful Change in the Specified PRO Endpoints

Score	Minimally important change (Improvement)	Minimally important change (Deterioration)	Minimally important difference	Meaningful within-patient change (Improvement)	Meaningful within-patient change (Deterioration)
4-item composite Dyspnea	-11	11	11	-8	8
QLQ-LC13 Cough	-21	15	18	-33	33
QLQ-LC13 Chest Pain	-26	24	26	-33	33
QLQ-C30 Global Health Status	8	-8	7	8	-8
QLQ-C30 Physical Functioning	8	-8	7	6	-13

Thresholds of clinical meaningfulness as defined by an anchor-based external analysis* of a blinded data-cut of the CodeBreaK 200 data, pre-defined prior to data unblinding. Minimally important change refers to a change within a group; minimally important difference refers to a change between groups.
*The anchor-based external analysis is described in Estimation of interpretative thresholds for patient-reported outcome scores: blinded analysis of Study 20190009 data. 20 August 2021; Adelphi values (data on file).

Source: de Langen et al, 2023

Figure 20. FACT-G and PRO-CTCAE Instruments: Change From Baseline to Week 12 (GEE Analysis)

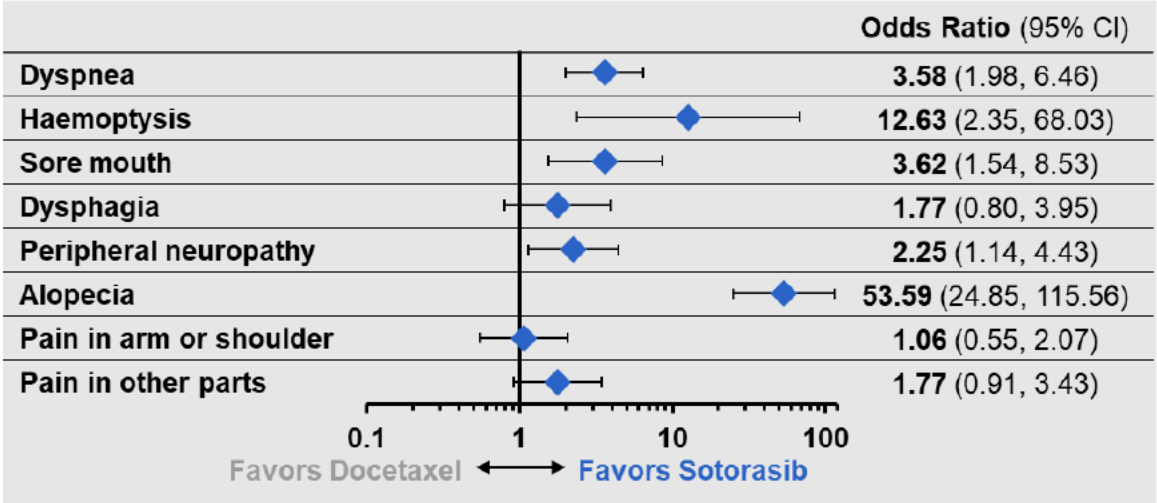


FACT-G = Functional Assessment of Cancer Therapy Tool - General form; GEE = generalized equation estimation; PRO-CTCAE = patient-reported outcome version of the Common Terminology Criteria for Adverse Events

Arrowheads indicated confidence intervals are wider than can be displayed in the graph

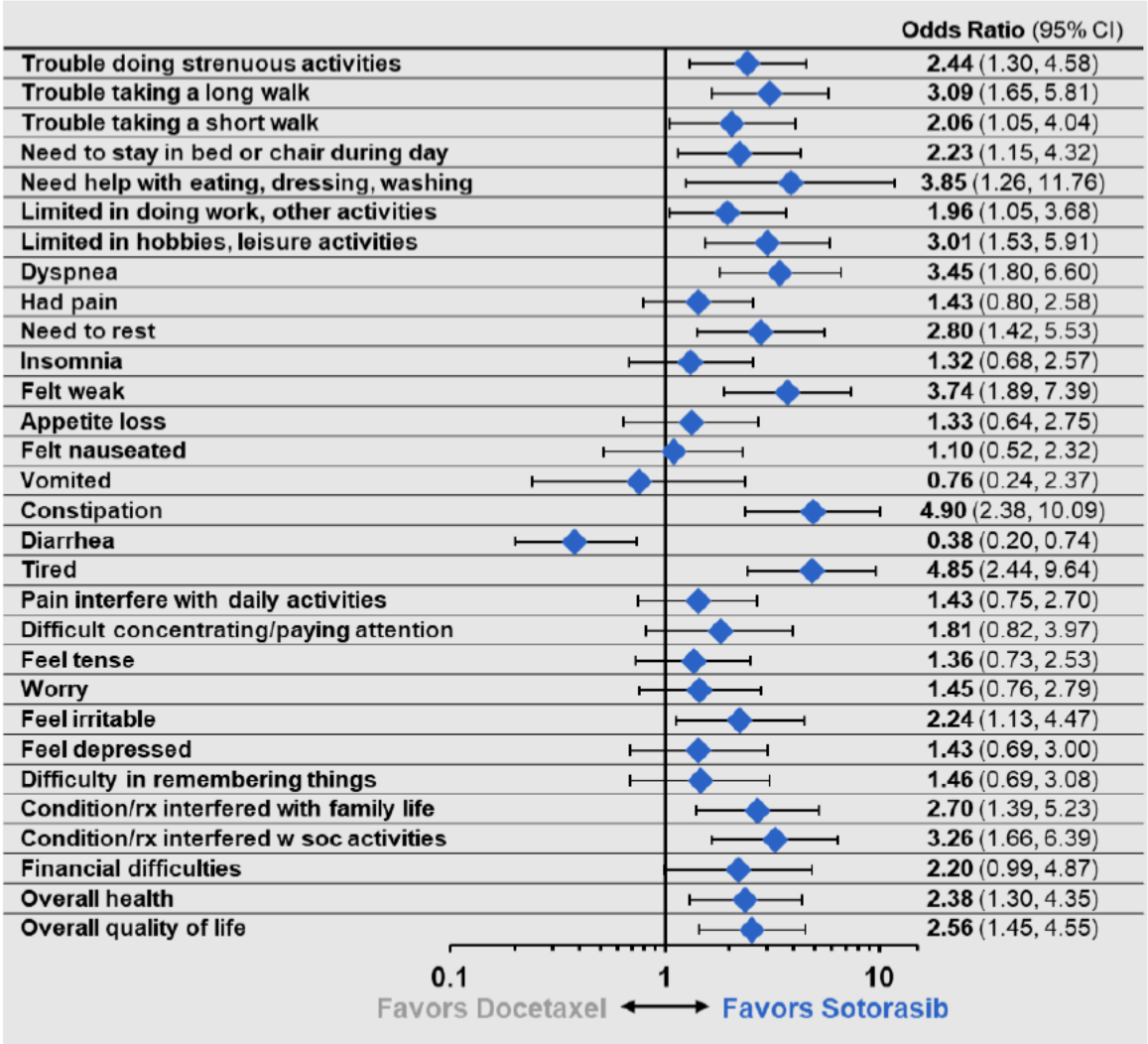
Source: Modified from Table 14-11-009-701, Table 14-11-008-703, Table 14-11-007-711, Table 14-11-007-712, and Table 14-11-007-710 of CodeBreaK 200 Primary Analysis

Figure 21. QLQ-LC13: Remaining Symptom Scales
GEE Model Change From Baseline to Week 12



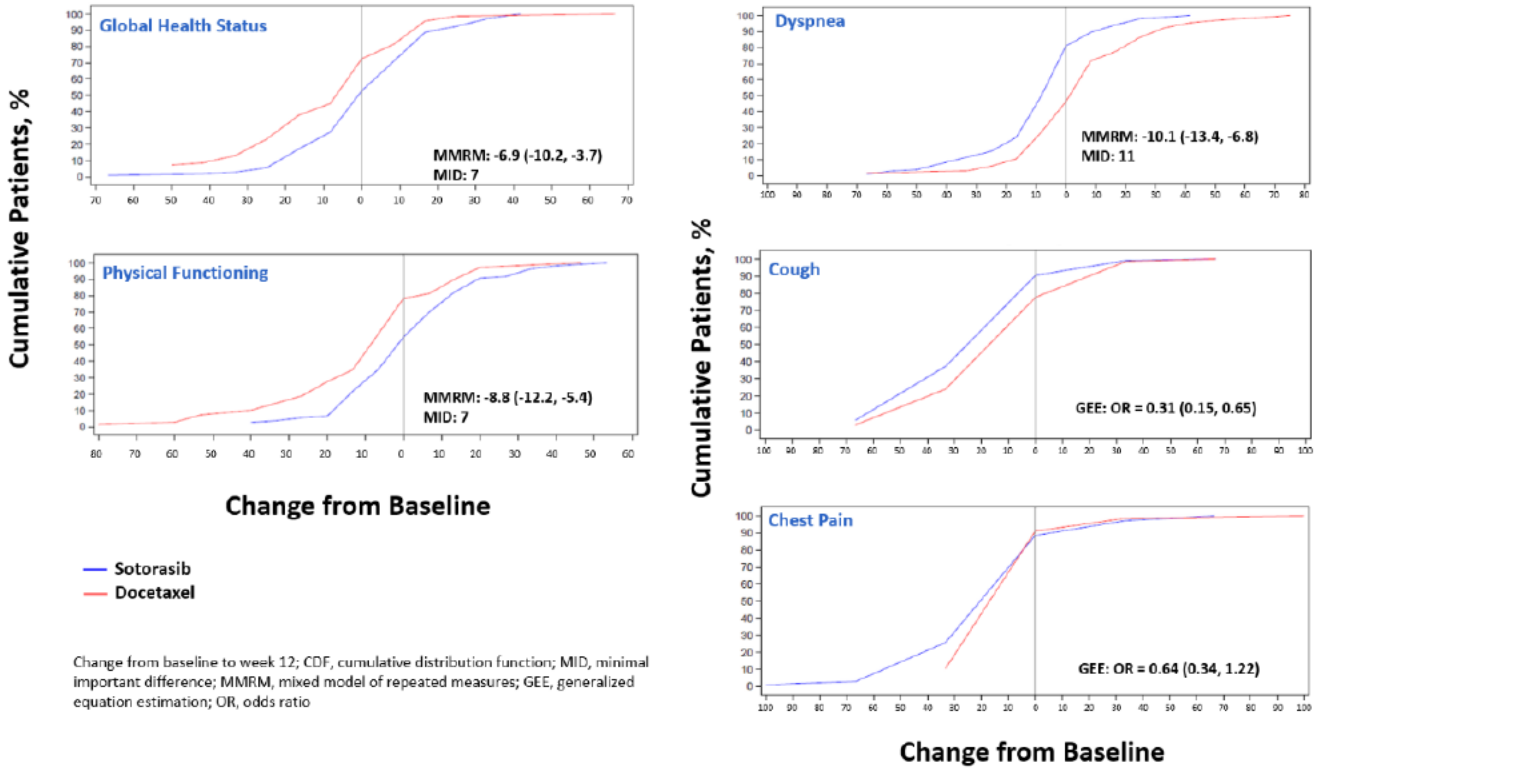
GEE = generalized equation estimation; QLQ-LC13 = quality of life questionnaire lung cancer module
Source: Modified from Table 14-11.3.802 and Table 90920230809-11.1.1 of CodeBreaK 200 Primary Analysis

Figure 22. QLQ-C30: Ordinal Symptom Scales
GEE Model Change From Baseline to Week 12



GEE = generalized equation estimation; QLQ-C30 = quality of life questionnaire 30-item core module
Source: Modified from Table 14-11.3.802, Table 90920230809-11.1.1, and Table 90920230809-11.1.6 of CodeBreaK 200 Primary Analysis

Figure 23. CDF Plot of Change From Baseline to Week 12 for EQ-5D-5L Visual Analog Score (EQ-5D-5L Analysis Set) (CodeBreaK 200 PFS Primary Analysis)



Change from baseline to week 12; CDF, cumulative distribution function; MID, minimal important difference; MMRM, mixed model of repeated measures; GEE, generalized equation estimation; OR, odds ratio

CDF = cumulative distribution function; EQ-5D-5L = EuroQol-5 Dimension 5 Level; GEE = generalized equation estimation
MID = minimal important difference; MMRM = mixed model of repeated measures; PFS = progression-free survival; OR = odds ratio
Notes: Data cut-off date = 02 August 2022 Only visits cycle 2 day 1, cycle 3 day 1, cycle 4 day 1, and cycle 5 day 1 are included in the analysis.
Source: Modified from Figure 14-11.4.701 of CodeBreaK 200 Primary Analysis

Appendix 5. Exposure-related Adverse Events (CodeBreaK 200)

Table 34. Summary of Incidence and Exposure-adjusted Rates of Treatment-related Adverse Events - Excluding Select PTs from Neoplasms SOC (Safety Analysis Set) (20190009 PFS Primary Analysis)

	Sotorasib (N = 169) n (%)/e [r]	Docetaxel (N = 151) n (%)/e [r]
Treatment-related treatment-emergent adverse events[a]	119 (70.4)/40.0 [297.3]	130 (86.1)/9.8 [1327.1]
Grade = 1	30 (17.8)/83.9 [35.8]	16 (10.6)/45.8 [34.9]
Grade = 2	33 (19.5)/93.7 [35.2]	53 (35.1)/34.8 [152.2]
Grade = 3	46 (27.2)/81.1 [56.7]	42 (27.8)/41.4 [101.4]
Grade = 4	9 (5.3)/102.8 [8.8]	17 (11.3)/47.6 [35.7]
Grade 3 and 4	55 (32.5)/79.2 [69.4]	59 (39.1)/38.6 [152.7]
Fatal adverse events	1 (0.6)/104.6 [1.0]	2 (1.3)/50.3 [4.0]
Grade ≥ 2	89 (52.7)/66.1 [134.6]	114 (75.5)/18.6 [614.0]
Grade ≥ 3	56 (33.1)/78.2 [71.6]	61 (40.4)/37.9 [160.9]
Grade ≥ 4	10 (5.9)/102.7 [9.7]	19 (12.6)/47.5 [40.0]
Serious adverse events	18 (10.7)/100.5 [17.9]	34 (22.5)/44.0 [77.3]
Leading to discontinuation of investigational product	16 (9.5)/104.5 [15.3]	17 (11.3)/49.4 [34.4]
Leading to dose reduction	26 (15.4)/86.6 [30.0]	40 (26.5)/36.2 [110.6]
Leading to dose interruption	60 (35.5)/77.8 [77.1]	23 (15.2)/45.3 [50.7]
Leading to dose interruption/reduction	67 (39.6)/71.9 [93.1]	53 (35.1)/32.7 [162.1]

Data cut-off date 02 August 2022.
N = Number of patients in the analysis set; n = Number of patients with observed data. Percentages are based on N.
e = Sum across all patients, the total time to first event or total exposure if no event (years).
r = Exposure-adjusted event rate per 100 patient years (n/e-yr*100).
Adverse events coded using MedDRA (version 25.0) and graded using CTCAE (version 5.0).
Multiple occurrences of the same event for a patient are counted as single events.
treatment emergent adverse event in this table are events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if patients cross over from docetaxel to sotorasib, whichever occurs earlier.
For patients with multiple events under the same category, only the worst grade is reported.
[a] Treatment-related adverse events are adverse events considered related to at least 1 study drug by the investigator.
Grade 5 fatal adverse events may start prior to data cutoff and result in death after data cutoff. These events are summarized in this table but the death after data cutoff are not included in analysis.
A list of select PTs within the neoplasms SOC have been excluded from this summary as they represent disease progression events

Source: Modified from Table 90920230616-06-003-002 of CodeBreaK 200 Primary Analysis

Appendix 6. Disease Progression MedDRA Preferred Terms

Table 35. Disease Progression Preferred Terms: CodeBreak 200

Preferred term
Non-small cell lung cancer
Lung adenocarcinoma
Lung neoplasm malignant
Non-small cell lung cancer metastatic
Adenocarcinoma
Metastases to spine
Neoplasm progression
Non-small cell lung cancer recurrent
Metastases to peritoneum
Tumour hyperprogression

Table 36. Disease Progression Preferred Terms: CodeBreak 100 Phase 2 Part B

Preferred term
Disease progression
Non-small cell lung cancer
Non-small cell lung cancer metastatic
Lung adenocarcinoma
Metastases to central nervous system
Lung neoplasm
Lung neoplasm malignant
Lymphangiosis carcinomatosa
Malignant neoplasm progression
Metastases to meninges

Appendix 7. Adverse Events in CodeBreaK 200 Without Exclusion of Disease Progression Terms

Table 37. Summary of Incidence of Treatment-emergent Adverse Events Including Disease Progression Preferred Terms (Safety Analysis Set) (Study 20190009 PFS Primary Analysis)

	Sotorasib (N = 169) n (%)	Docetaxel (N = 151) n (%)
All treatment-emergent adverse events	166 (98.2)	148 (98.0)
Grade ≥ 2	152 (89.9)	136 (90.1)
Grade ≥ 3	121 (71.6)	91 (60.3)
Grade ≥ 4	48 (28.4)	35 (23.2)
Serious adverse events	91 (53.8)	67 (44.4)
Leading to discontinuation of investigational product	28 (16.6)	24 (15.9)
Leading to dose reduction	26 (15.4)	43 (28.5)
Leading to dose interruption	86 (50.9)	42 (27.8)
Fatal adverse events	37 (21.9)	18 (11.9)
Treatment-related treatment-emergent adverse events[a]	119 (70.4)	130 (86.1)
Grade ≥ 2	89 (52.7)	114 (75.5)
Grade ≥ 3	56 (33.1)	61 (40.4)
Grade ≥ 4	10 (5.9)	19 (12.6)
Serious adverse events	18 (10.7)	34 (22.5)
Leading to discontinuation of investigational product	16 (9.5)	17 (11.3)
Leading to dose reduction	26 (15.4)	40 (26.5)
Leading to dose interruption	60 (35.5)	23 (15.2)
Fatal adverse events	1 (0.6)	2 (1.3)

CTCAE = Common Terminology Criteria for Adverse EventsMedDRA = Medical Dictionary for Regulatory Activities; PFS = progression-free survival; N = number of patients in the analysis set; n = number of patients with observed data

Data cut-off date = 02 August 2022

Adverse events coded using MedDRA (version 25.0) and graded using CTCAE (version 5.0). Treatment-emergent adverse events in this table are events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if patients crossed over from docetaxel to sotorasib, whichever occurred earlier. For patients with multiple events under the same category, only the worst grade was reported. Grade 5 fatal adverse events may have started before data cut-off and resulted in death after data cut-off. These events are summarized in this table, but deaths after data cut-off are not included in analysis.

[a] Treatment-related adverse events are adverse events considered related to at least 1 investigational product by the investigator.

Source: Modified from Table 14-6.1.1 of CodeBreaK 200 Primary Analysis

Table 38. Treatment-emergent Fatal Adverse Events by Preferred Term Including Disease Progression Preferred Terms (Safety Analysis Set) (Study 20190009 PFS Primary Analysis)

Preferred Term	Sotorasib (N = 169) n (%)	Docetaxel (N = 151) n (%)
Number of patients reporting treatment-emergent fatal adverse events	37 (21.9)	18 (11.9)
Non-small cell lung cancer	17 (10.1)	5 (3.3)
Lung adenocarcinoma	2 (1.2)	1 (0.7)
Lung neoplasm malignant	2 (1.2)	0 (0.0)
Non-small cell lung cancer metastatic	2 (1.2)	0 (0.0)
Cardiac arrest	1 (0.6)	1 (0.7)
Multiple organ dysfunction syndrome	1 (0.6)	1 (0.7)
Acute kidney injury	1 (0.6)	0 (0.0)
Adenocarcinoma	1 (0.6)	0 (0.0)
COVID-19 pneumonia	1 (0.6)	0 (0.0)
Colitis	1 (0.6)	0 (0.0)
Delirium	1 (0.6)	0 (0.0)
Disseminated intravascular coagulation	1 (0.6)	0 (0.0)
Dyspnoea	1 (0.6)	0 (0.0)
Interstitial lung disease	1 (0.6)	0 (0.0)
Metastases to spine	1 (0.6)	0 (0.0)
Non-small cell lung cancer recurrent	1 (0.6)	0 (0.0)
Pneumonia	1 (0.6)	0 (0.0)
Pulmonary embolism	1 (0.6)	0 (0.0)
Respiratory failure	0 (0.0)	2 (1.3)
Abdominal pain	0 (0.0)	1 (0.7)
Altered state of consciousness	0 (0.0)	1 (0.7)
Cerebrovascular accident	0 (0.0)	1 (0.7)
Ileus	0 (0.0)	1 (0.7)
Pneumonia aspiration	0 (0.0)	1 (0.7)
Respiratory depression	0 (0.0)	1 (0.7)
Seizure	0 (0.0)	1 (0.7)
Tumour hyperprogression	0 (0.0)	1 (0.7)

MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the analysis set; n = number of patients with observed data; PFS = progression-free survival

Notes: Data cut-off date = 02 August 2022.

Adverse events are coded using MedDRA (version 25.0). Treatment-emergent adverse events in this table are events with onset after the administration of the first dose of any study treatment and within the end of study, or 30 days after the last dose of any study treatment, or before the first dose of sotorasib if patients crossed over from

Source: Modified from Table 14-6.5.1 of of CodeBreaK 200 Primary Analysis

Appendix 8. Studies Contributing to Integrated Safety Analysis

Table 39. Clinical Studies Contributing to the Integrated Analysis of Safety

Study Number	Study Objective(s)	Study Design and Type of Control	Dosage and Dosage Regimen	Number of Patients Enrolled	Data cut off
20190009 (CodeBreaK 200)	Efficacy, safety, tolerability, PROs, PK	Phase 3 multicenter, randomized, open-label, active-controlled	Sotorasib 960 mg PO QD Docetaxel 75 mg/m^2 IV Q3W	345 (171 sotorasib; 174 docetaxel)	02 August 2022
20170543 (CodeBreaK 100)	Phase 1 Safety, tolerability, efficacy, PK, PD Phase 2 Safety, tolerability, efficacy, PK, PD, PRO	Phase 1/2 monotherapy and in combination, nonrandomized, open-label, dose exploration	Sotorasib monotherapy treatment groups Phase 1 Part 1a: 180, 360, 720, or 960 mg QD Parts 1b and 2b: 480 mg BID with food Parts 1d and 2d: 960 mg QD with food Parts 2a and 2e: 960 mg QD Phase 2 Part A: 960 mg QD Part B: 960 or 240 mg QD	Monotherapy treatment groups only: Phase 1 Part 1: 88 (including backfill) Part 2: 134 Phase 2 Part A: 252 Part B: 209 (104 at 960 mg; 105 at 240 mg)	02 August 2022 (phase 1 and phase 2 part A) 09 September 2022 (phase 2 part B)
20190135 (CodeBreaK 101) Subprotocol G	Safety, tolerability, PK, efficacy	Phase 1b open-label	Sotorasib 960, 480, or 240 mg QD	6	02 August 2022
20190147 (CodeBreaK 105)	Safety, tolerability, PK, efficacy in Chinese patients	Phase 1 open-label	Sotorasib 720 or 960 mg QD	12	02 August 2022

BID = twice daily; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; PO = administered orally; PRO = patient-reported outcome; QD = once daily; Q3W = every 3 weeks