FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

October 5, 2023

NDA 214665 s005

Sotorasib

Amgen, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the sotorasib new drug application (NDA) 214665 supplement 005 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Anti-PD-(L)1	Anti-PD-1/anti-PD-L1
ASCO	American Society of Clinical Oncology
BICR	Blinded independent central review
CI	Confidence Interval
CNS	Central nervous system
COP	Confirmation of progression
DCO	Data cutoff
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FAS	Full analysis set
FDA	Food and Drug Administration
FDCA	Food, Drug, and Cosmetic Act
GDP	guanosine diphosphate
GTP	Guanosine triphosphate
HR	Hazard ratio
IA	Interval analysis
IASLC	International Association for the Study of Lung Cancer
iDMC	Independent data monitoring committee
IND	Investigational new drug
ITT	Intention-to-treat
IV	intravenous
KRAS	Kirsten rat sarcoma viral oncogene homolog
MMRM	Model for repeated measures
mOS	Median overall survival
mPFS	Median progression-free survival
NDA	New drug application
NSCLC	Non-small cell lung cancer
ODAC	Oncologic Drugs Advisory Committee
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PMR	Post marketing requirement
PFS	Progression-free survival
PI	Principal investigator
PRO	Patient reported outcome
QLQ-C30	Quality-of-Life Questionnaire Core 30
QLQ-LC13	Quality-of-Life Questionnaire Core 13

RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAP	Statistical analysis plan
SAS	Safety analysis set
SMP	Study May Proceed
sNDA	Supplemental new drug application
TEAE	Treatment-emergent adverse effect

1. EXECUTIVE SUMMARY

1.1 Sotorasib Development History

Sotorasib (LUMAKRAS) is an oral targeted therapy intended to treat patients with *Kirsten rat sarcoma viral oncogene homolog (KRAS) G12C* mutations.

On May 28, 2021, sotorasib was granted accelerated approval for the treatment of patients with *KRAS G12C*-mutated non-small cell lung cancer (NSCLC), who had received at least one prior systemic therapy. Approval was based on CodeBreaK 100, a single-arm trial in patients with locally advanced or metastatic NSCLC with *KRAS-G12C* mutations. The main efficacy outcome measures were objective response rate (ORR) according to RECIST 1.1, as evaluated by blinded independent central review (BICR) and duration of response (DOR). The ORR was 36% (95% confidence interval [CI]: 28%, 45%), with a median DOR of 10 months (range 1.3+, 11.1)[1].

Prior to the sotorasib accelerated approval, a preferred standard of care regimen for patients with *KRAS G12C*-mutated NSCLC who had progressed on at least one prior systemic therapy was single agent docetaxel, with a historical ORR of approximately 12%[,2].

Given the longstanding knowledge of the *KRAS G12C* mutation in approximately 13% of patients with nonsquamous NSCLC[3], and the multiple failed attempts to develop effective drugs in this space, the early promising results of CodeBreaK 100 were met with great enthusiasm by the oncology community.

As part of the Postmarketing Requirement (PMR) to verify the clinical benefit of sotorasib, Amgen Inc. (“Applicant”) conducted CodeBreaK 200, an open-label clinical trial, which randomized patients 1:1 to receive either single agent oral sotorasib or single agent intravenous (IV) docetaxel. FDA acknowledges the obligatory nature of the open label design, given the routes of administration (oral vs IV) and differing toxicity profiles. The primary endpoint was progression-free survival (PFS) by BICR. Overall survival (OS) was a secondary endpoint. Crossover was not permitted at the time of trial initiation but was later instituted in Protocol Amendment 3.

Public awareness and enthusiasm for sotorasib was evident before initiation of CodeBreaK 200 and continued throughout the course of the trial. Press releases regarding the therapeutic benefit of sotorasib were issued as early June 3, 2019, almost one year before the first patient enrolled onto CodeBreaK 200.

At the time of the new drug application (NDA) submission for accelerated approval based on CodeBreaK 100 on December 16, 2020, 41% of patients were enrolled to CodeBreaK 200. Enrollment of CodeBreaK 200 was complete by the time of the accelerated approval of sotorasib.

On February 24, 2023, the Applicant submitted a supplemental NDA (sNDA) for the conversion from accelerated approval to traditional approval for sotorasib, based on CodeBreaK 200.

The top line results of CodeBreaK 200 are presented in Table 1:

Table 1: Summary of Efficacy Results for CodeBreaK 200

	Sotorasib N = 171	**Docetaxel N = 174**
Median PFS per BICR, months (95% CI)	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)
PFS events, n (%)	122 (71)	101 (58)
HR (95% CI)	0.66 (0.51, 0.86)	
p-value	0.002	
Median OS, months (95% CI)	10.6 (8.9, 14.0)	11.3, (9.0, 14.9)
Deaths, n (%)	109 (64)	94 (54)
HR (95% CI)	1.01 (0.77, 1.33)	
p-value	0.53	
Crossover from docetaxel to sotorasib, n (%)	46 (26)	
ORR per BICR, % (95% CI)	28 (22, 35)	13 (9, 19)
Odds ratio (95% CI)	2.60 (1.48, 4.56)	
p-value	<0.001	
Median DOR, months (range)	8.6 (6.9, 12.3)	6.8 (4.3, 8.3)

Data cutoff (DCO) date: August 2, 2022.
Source: FDA review based on datasets submitted in NDA 214665 s005.

1.2 Concerns for Systemic Bias and Study Conduct Issues

Upon initial receipt of this top line data, FDA noted the median PFS benefit of approximately 5 weeks was less than the standard imaging interval of 6 weeks. This finding raised concerns for variability in the median PFS result given interval censoring. In CodeBreaK 200, both the FDA and the Applicant report that the median PFS benefit in CodeBreaK 200 could be as little as 5 days. This coupled with equivocal OS results, raised questions about the clinical significance of CodeBreaK 200.

In terms of patient disposition, it was observed that 23 patients in the docetaxel arm, were randomized and never treated, relative to 2 patients in the sotorasib arm who were randomized and never treated. This asymmetric early withdrawal of patients in the docetaxel group, was one of the first indications of possible systemic bias in CodeBreaK 200.

Upon further review, the FDA review team investigated multiple sources of potential systemic bias in this open-label trial which will be further described herein. To summarize, the FDA observed the following:

a) Asymmetric early dropout, with greater dropout on the docetaxel arm
b) Investigator assessments of progressive disease favoring the sotorasib arm
c) Crossover of patients from docetaxel to sotorasib before assessment of disease progression by BICR

Further issues related to study conduct included a lack of adherence to the imaging charter. Multiple imaging assessments were conducted by the BICR to resolve discrepancies between investigator and BICR assessments, which was considered a protocol violation, triggering additional concern regarding data quality and integrity.

In summary, CodeBreaK 200 was a trial designed to verify the clinical benefit of single agent sotorasib vs docetaxel, after the initial accelerated approval of sotorasib based on single arm data yielding an ORR of 36% (95% CI: 28%, 45%).

However, the trial results are confounded by multiple sources of systemic bias, raising concerns about whether CodeBreaK 200 can be considered an adequate and well-controlled trial. Furthermore, the primary endpoint of PFS by BICR may not be reliable, given its magnitude relative to the imaging interval (5 weeks vs 6 weeks).

While the Applicant asserts that the hazard ratio (HR) ranging from 0.60 to 0.72 is robust and maintained through multiple sensitivity analyses, the FDA posits that other measures of treatment effect, such as PFS event rate, difference in median PFS, and shape of the Kaplan-Meier curves are critical in measuring treatment benefit. Additionally, treatment benefit must be reinforced by the results of additional endpoints such as overall survival.

It should be noted that the overall response rates throughout CodeBreaK 100 and 200 are relatively consistent, suggesting a consistent anti-tumor effect in terms of ORR. However, in the context of CodeBreaK 200, the primary hypothesis being tested was whether sotorasib demonstrates a PFS benefit over docetaxel.

1.3 Regulatory Considerations

Is CodeBreaK 200 an adequate and well-controlled trial?

The FDA is convening this Oncologic Drugs Advisory Committee (ODAC) to discuss whether CodeBreaK 200 can be considered an adequate and well-controlled trial, given the multiple indications of systemic bias observed related to study conduct.

In order to be considered an adequate and well-controlled trial, a clinical trial should include:

a) A clear statement of objectives and methods of analysis
b) A study design that permits a valid comparison with a control

c) Adequate measures to minimize bias in subject assignment to treatment group, to assure comparability of the groups
d) Adequate measures to minimize bias on the part of subjects, observers, and analysts of the data
e) Well-defined and reliable methods to assess response
f) Adequate analysis of the results of the study to assess the effect of the drug[4]

Given the high rate of early dropout on the docetaxel arm and potential loss of randomization, there were not adequate measures in place to minimize bias in patient assignment to treatment group, to assure comparability of the groups. **(c/d)**

Adequate measures were either not put in place, or not adequately followed to minimize bias on the part of investigators, given the rates of discrepancy between investigator and BICR calls for progression. Investigators, and likely patients as well, were eager to access sotorasib given its early success and differing route of administration and toxicity profile. **(d)**

Violations of the imaging charter, with confirmation of progression (COP) indirectly used to audit certain BICR assessments resulting in multiple sets of BICR reads, suggest that there were not well defined and reliable methods to assess response. **(e)**

Ultimately, issues in study conduct, high rates of censoring, loss of follow up of patients who withdrew consent, and potential loss of randomization may not allow for adequate analysis of the results of CodeBreaK 200 to assess the effect, and importantly the magnitude of effect, of sotorasib vs docetaxel. **(f)**

1.4 Discussion at the Oncologic Drugs Advisory Committee Meeting

The committee will not be asked to opine on whether CodeBreaK 200 should serve as a basis for conversion of sotorasib from accelerated to traditional approval.

Rather, the committee will be asked to discuss if the results of CodeBreaK 200 can be reliably interpreted, and whether CodeBreaK 200 can be considered an adequate and well-controlled trial.

2. INTRODUCTION AND BACKGROUND

2.1 Rationale for Sotorasib in NSCLC and Unmet Need

Metastatic *KRAS-G12C* mutated NSCLC is a genetically distinct form of lung cancer that is not curable with available therapy[5]. The *KRAS G12C* mutation results in the accumulation of the active form of the KRAS protein, leading to downstream

proliferative and survival signaling and uncontrolled cell growth[6,7]. The *KRAS G12C* mutation occurs in approximately 13% of patients with lung adenocarcinoma[3].

KRAS was long considered an “undruggable" target for much of the last four decades since its discovery[8]. This lack of progress in targeting the protein was due to a variety of factors, including affinity of KRAS for guanosine triphosphate (GTP) and high intracellular concentrations of GTP, both contributing to higher concentrations of the active GTP-bound KRAS, and the smooth surface of the protein lacking binding sites[9,10]. The discovery of the switch pocket II of the KRAS protein was the breakthrough that led to the development of molecules specifically targeting the cysteine residue in KRAS G12C mutant proteins, thereby trapping the protein in the inactive, guanosine diphosphate (GDP)-bound state, preventing downstream proliferation and signaling[11,12].

For first-line metastatic disease, the treatment paradigms for patients with *KRAS-G12C* mutations are the same as for patients without actionable genomic alterations. Approximately 40 – 50% of patients with advanced NSCLC will respond to first-line chemotherapy/immunotherapy combinations. However, most patients will progress on or after standard first-line therapies[13]. Prior to the accelerated approvals of sotorasib and adagrasib, another KRAS G12C inhibitor, preferred second-line treatment options have included docetaxel as a single agent or in combination with ramucirumab[14,15].

Table 2 provides a summary of FDA-approved second-line or later treatments for patients with *KRAS G12C*-mutated NSCLC, after disease progression on platinum-based chemotherapy and an anti-PD-(L)1 antibody.

Table 2: FDA Approved Therapies for *KRAS G12C*-Mutated, Metastatic NSCLC After Prior Platinum Chemotherapy and Anti-PD-(L)1 Based Therapy

Drug	Indication	Selected Efficacy Results
Small molecule targeted therapy		
Sotorasib*	*KRAS G12C*-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy	ORR 36% (95% CI: 28%, 45%)[1]
Adagrasib*	*KRAS G12C*-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy	ORR 43% (95% CI: 34%, 53%)[16]
Single-agent chemotherapy		
Docetaxel	Locally advanced or metastatic NSCLC after platinum therapy failure	ORR 12% (95% CI: 9, 17) mPFS 4.2 months (95% CI: 3.5, 4.9) mOS 9.4 months (95% CI: 8.1, 10.7)[14]
Pemetrexed	Locally advanced or metastatic non-squamous NSCLC after prior chemotherapy	ORR 9% (95% CI: 6, 13) mPFS 2.9 months (95% CI: 2.4, 3.1) mOS 8.3 months (95% CI: 7.0, 9.4)[17]
Combination chemotherapy		
Docetaxel plus ramucirumab	Metastatic NSCLC with disease progression on or after platinum-based chemotherapy	ORR 23% (95% CI: 20, 26) mPFS 4.5 months (95% CI: 4.2, 5.4) mOS 10.5 months (95% CI: 9.5, 11.2)[15]

Source: FDA review.

* Sotorasib and adagrasib are under accelerated approval and therefore are not considered available therapy per FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, May 2014

2.2 REGULATORY HISTORY

Sotorasib was granted accelerated approval for the treatment of patients with *KRAS G12C*-mutated NSCLC, who had received at least one prior systemic therapy on May 28, 2021. The approval was based on results of the single-arm CodeBreaK 100 trial of sotorasib which demonstrated an ORR of 36% (95% CI: 28%, 45%) with a median DOR of 10 months (range 1.3+, 11.1)[1].

The following PMR was issued for sotorasib:

> Conduct a multicenter, randomized clinical trial and submit the final progression-free survival (PFS) results that verify and describe the clinical benefit of sotorasib in patients with locally advanced or metastatic non-small cell lung cancer with a history of prior systemic therapy for advanced disease and whose tumors harbor *Kirsten rat sarcoma (KRAS) G12C* mutation.

FDA also determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) would not be sufficient to assess a known risk of adverse events including gastrointestinal toxicity in patients receiving sotorasib. Therefore, the following additional PMR was issued for sotorasib:

> Conduct a multicenter, randomized clinical trial to further characterize serious adverse events, including gastro-intestinal toxicity and compare the safety and efficacy of sotorasib 960 mg daily versus a lower daily dose in patients with locally advanced or metastatic, *KRAS G12C* mutated, non-small cell lung cancer who have received at least one prior systemic therapy.

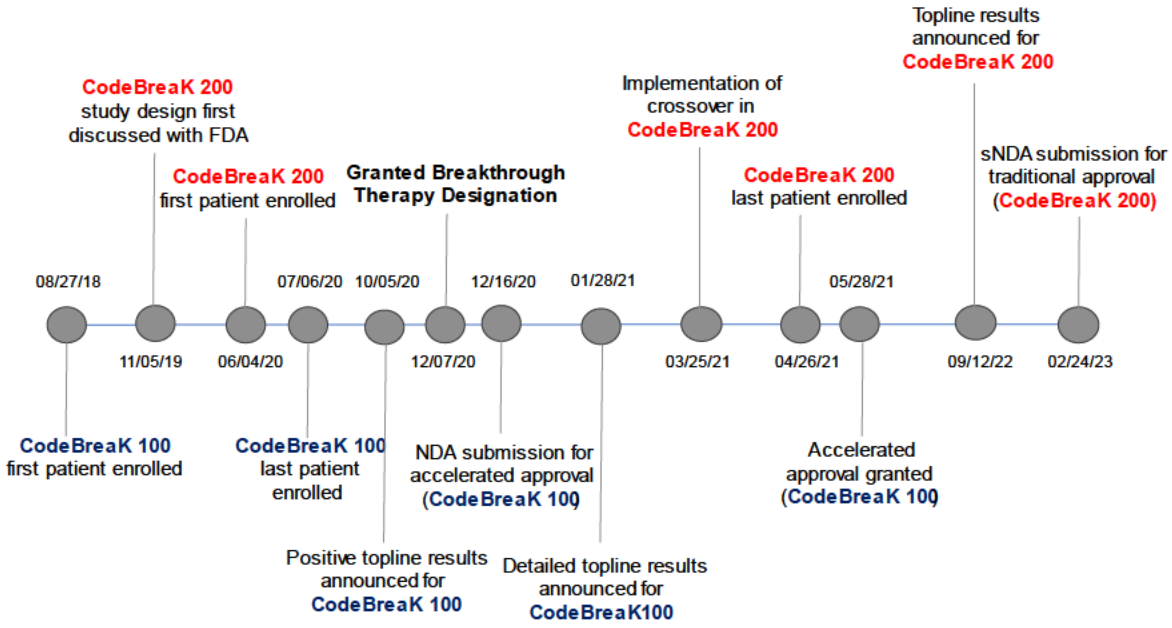
As part of the Applicant's PMR to verify and describe the clinical benefit of sotorasib, the Applicant conducted CodeBreaK 200, an open-label clinical trial, which randomized patients 1:1 to receive either single agent sotorasib or single agent IV docetaxel.

Press releases regarding the therapeutic benefit of sotorasib were issued as early as June 3, 2019, almost one year before the first patient enrolled onto CodeBreaK 200. At the time of submission of the NDA for accelerated approval based on CodeBreaK 100 on December 16, 2020, 41% of patients were enrolled to CodeBreaK 200. On February 24, 2023, the Applicant submitted an sNDA for the conversion from accelerated approval to traditional approval for sotorasib, based on CodeBreaK 200.

More detailed regulatory interactions are described in Figure 1 and Table 3.

The clinical development timeline of sotorasib is shown in Figure 1 below:

Figure 1: Clinical Development Timeline of Sotorasib



Source: FDA review.

Table 3 provides summaries of the key regulatory interactions between FDA and the Applicant regarding the development of sotorasib.

Table 3: Key Regulatory History for Sotorasib

Date	Discussion
June 29, 2018	FDA issued "Study May Proceed" (SMP) letter for initiation of CodeBreaK 100
August 16, 2019	FDA granted Fast Track Designation to sotorasib for the treatment of patients with previously treated metastatic NSCLC with a *KRAS G12C* mutation
November 5, 2019	Type B pre-investigational new drug (IND)/pre-Phase 3 meeting between FDA and the Applicant to discuss the design of CodeBreaK 200. FDA found the proposed study design generally acceptable but expressed concerns that the targeted 3.2-month difference in median PFS would not be considered clinically meaningful. The Applicant stated that the 3.2-month difference is the minimal detectable difference, but that the extent of improvement is expected to be much greater. FDA

	recommended that the Applicant modify CodeBreaK 200 to assess OS as a primary endpoint. FDA advised that in order to potentially support a marketing application based on an improvement in PFS, the magnitude of effect on PFS would need to be considered clinically meaningful or be supported by a statistically significant difference in OS.
December 7, 2020	FDA granted Breakthrough Therapy Designation to sotorasib for the treatment of patients with locally advanced or metastatic NSCLC with a *KRAS G12C* mutation, based on the CodeBreaK 100 results
December 16, 2020	NDA submission for accelerated approval for sotorasib based on CodeBreaK 100 In total, 41% of patients had been enrolled to the confirmatory CodeBreaK 200 trial at the time of the NDA submission based on CodeBreaK 100
January 30, 2021	Topline results for CodeBreaK 100 publicly announced at the International Association for the Study of Lung Cancer (IASLC) World Lung Conference.
February 9, 2021	Type B guidance meeting between FDA and the Applicant to discuss changes to the statistical analysis plan (SAP) for CodeBreaK 200 based on concerns for equipoise and ensuring access to sotorasib for patients who progressed on docetaxel. The FDA and the Applicant discussed the following potential modifications to the SAP: • Allowing crossover to minimize patient dropout • Sample size recalculation based on PFS events alone • Maintaining Type 1 error control for OS, but decreasing power • Consideration of implementing an early stopping rule for futility in the docetaxel arm and/or a 2:1 randomization scheme to maximize the number of patients receiving sotorasib. The Applicant proposed reduction of the sample size from 650 patients to 330 patients, while maintaining a 1:1 randomization scheme, a plan to conduct an interim analysis (IA) at an information fraction of approximately 70% (observation of 160 events), and allowance of crossover from the docetaxel group.
February 15, 2021	Protocol Amendment 3 to CodeBreaK 200, instituting changes to SAP noted above.

March 25, 2021	First implementation of crossover in CodeBreaK 200 at clinical trial site.
April 26, 2021	Last patient enrolled on CodeBreaK 200
May 28, 2021	FDA granted accelerated approval for sotorasib for the treatment of patients with locally advanced or metastatic NSCLC with a *KRAS G12C* mutation, based on the results of CodeBreaK 100
April 5, 2022	The Applicant provided FDA with an updated interim PFS analysis at 74% information fraction with a data cutoff (DCO) date of October 5, 2021. The interim PFS per BICR results were not initially statistically significant. However, after noting a discrepancy between investigator and BICR assessments, the Applicant notified the imaging vendor, (b) (4). The (b) (4) BICR radiologists re-read discordant scans which led to updated PFS results which were then deemed to be statistically significant, based on changed readings of 12 scans. See Section 4.6 for additional details.
May 5, 2022	Ad hoc meeting between FDA and the Applicant to discuss updated PFS interim analysis results and BICR re-reads. FDA expressed concerns regarding lack of adherence to the protocol and imaging charter. The Applicant requested submission of a marketing application based on this interim PFS analysis, however FDA advised against this submission and instead recommended a global re-read of all scans given concerns for study integrity.
October 21, 2022	Type B pre-sNDA meeting between FDA and the Applicant to discuss results of CodeBreaK 200 and plan for sNDA submission.
February 24, 2023	Supplemental NDA submission for conversion of sotorasib from accelerated to traditional approval based on the results of CodeBreaK 200

Source: FDA review.

2.3 Public Interest in Sotorasib

Public awareness and enthusiasm for sotorasib was evident at the time of initiation of CodeBreaK 200 and throughout the course of the trial. At the onset, sotorasib was a novel therapy against a previously “undruggable” target and docetaxel had a historically poor response rate. On October 5, 2020, within three months of initiation of CodeBreaK 200, the Applicant issued a press release indicating “durable anticancer activity” was

observed for sotorasib in CodeBreaK 100. On December 7, 2020, FDA granted sotorasib Breakthrough Therapy Designation which is reserved for drugs that have preliminary clinical evidence demonstrating a potential substantial improvement over available therapy. Topline results for CodeBreaK 100 were announced on January 30, 2021, at the Presidential Symposium for IASCL World Conference. Public awareness and interest in sotorasib was evident throughout enrollment of CodeBreaK 200 which may have made the trial more susceptible to open-label bias.

Selected Applicant press releases for sotorasib in NSCLC, which may have contributed to study conduct issues for CodeBreaK 200, include the following:

- June 3, 2019: First sotorasib clinical data announced at American Society of Clinical Oncology (ASCO) Conference 2019
- May 29, 2020: New sotorasib clinical data announced at ASCO Conference 2020
- September 20, 2020: Clinical data from CodeBreaK 100 published in New England Journal of Medicine
- October 5, 2020: Positive topline results announced for Phase 2 (NSCLC) Cohort of CodeBreaK 100
- December 8, 2020: Breakthrough Therapy Designation announced for NSCLC
- December 16, 2020: Submission of NDA for sotorasib in NSCLC announced
- January 28, 2021: Detailed topline results announced for Phase 2 (NSCLC) Cohort of CodeBreaK 100 stating "…sotorasib demonstrated rapid, deep, and durable responses…". Results presented at the IASLC World Lung Conference 2020[18]

3. STUDY 20190009 (CodeBreaK 200)

3.1 Study Design

CodeBreaK 200 (Study 20190009) is an ongoing, multicenter, randomized, open-label, active-controlled trial to evaluate the efficacy and safety of sotorasib versus docetaxel in patients with previously treated, locally advanced and unresectable or metastatic NSCLC with a *KRAS G12C* mutation. In total, 345 patients were randomized 1:1 to receive oral sotorasib 960 mg once daily (171 patients) or IV docetaxel 75 mg/m^2 every 3 weeks (174 patients). Patients were stratified at randomization by number of prior lines of therapy for advanced disease (1 vs 2 vs > 2), race (Asian vs non-Asian), and history of central nervous system (CNS) involvement (present vs absent).

Radiographic tumor assessments were conducted at screening, every six weeks through week 49, then at nine-week intervals thereafter. Patients were to receive treatment until independent central confirmation of progression, intolerance of treatment

leading to discontinuation, initiation of another anticancer therapy, or withdrawal of consent.

Crossover from docetaxel to sotorasib was instituted with Protocol Amendment 3 (February 15, 2021), with 99% of patients enrolled before Protocol Amendment 3 was implemented at their respective trial sites.

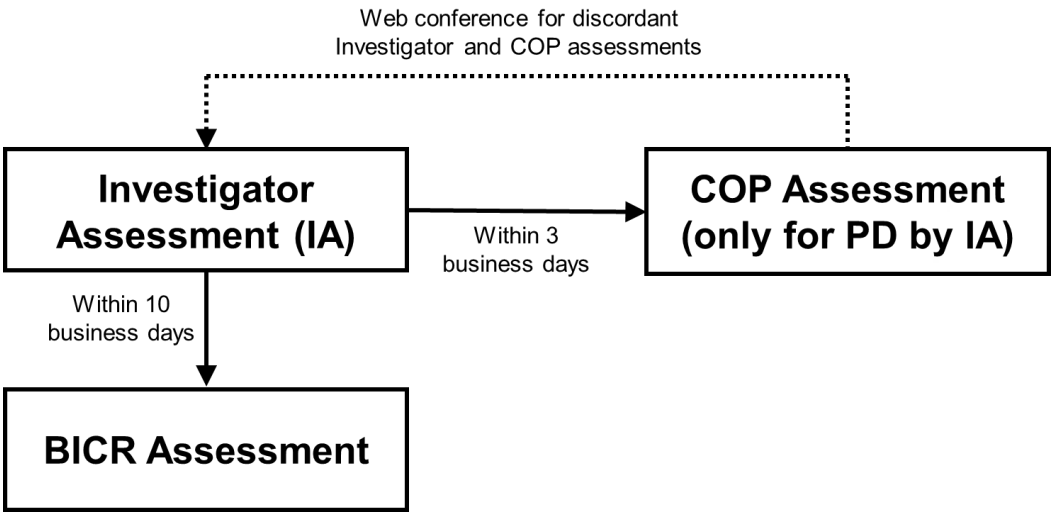
Per protocol, once a patient was determined to have radiologic progression by the investigator, they were given the opportunity to either:

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

The Applicant's Briefing Document indicates the above procedure also required independent central review prior to continuing therapy beyond disease progression or crossing over to sotorasib for patients on the docetaxel arm. However, FDA clarifies this independent central review process was by a COP procedure, rather than BICR. BICR assessment or confirmation of disease progression is often a requirement in trials allowing for crossover from the control arm to investigational product; this criterion minimizes missing assessments in a BICR-assessed PFS endpoint when crossover is a feature of a trial. The COP procedure was completely different and separate from the BICR assessment of radiographic disease progression, as discussed below.

A COP procedure was implemented once crossover was built into the protocol with Protocol Amendment 3. The COP procedure required an independent COP radiologist (separate from the BICR radiologist) to review scans within three business days after an investigator made an assessment of disease progression. The purpose of the COP reading was to provide the site investigators with a second independent opinion regarding whether the patient had progressive disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). If the COP radiologist did not agree with the assessment of disease progression, a web conference could be organized between the investigators and the COP radiologist to resolve any discordant reads. Confirmation of progression was required for patients to receive treatment beyond progression or for patients on the docetaxel arm to crossover over to receive sotorasib on the trial. However, investigators would make the final treatment and patient management decisions. Figure 2 shows the schema for the COP procedure.

Figure 2: Confirmation of Progression Procedure in CodeBreaK 200



Source: FDA review.

See Section 4.6 for additional details about the COP procedure and its impact on interpreting the trial results.

Primary Endpoint: PFS per RECIST v1.1 as assessed by BICR.

Secondary Endpoints:

- OS
- ORR
- Patient reported outcomes (PROs) measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 13 (QLQ-LC13) and the EORTC Quality-of-Life Questionnaire Core 30 (QLQ-C30).

Key inclusion criteria for CodeBreaK 200:

- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
- Histologically or pathologically documented, locally advanced and unresectable or metastatic NSCLC with documentation of *KRAS p.G12C* mutation confirmed by central testing through the current protocol
- Progression or disease recurrence on or after receiving at least one prior systemic therapy for locally advanced and unresectable or metastatic disease. Prior treatment must include a platinum-based doublet chemotherapy and checkpoint inhibitor, either given as one line of therapy or as individual lines of therapy, unless the patient has a medical contraindication to one of the required therapies

- Measurable disease per RECIST v1.1 criteria.

Key exclusion criteria for CodeBreaK 200:

- Prior treatment with docetaxel in the unresectable or metastatic setting
- Prior treatment with sotorasib or another KRAS G12C inhibitor
- Previously identified driver mutation other than *KRAS G12C* for which an approved therapy is available.

3.2 Statistical Analysis Plan

The SAP for CodeBreaK 200 was originally designed with 650 patients randomized 1:1, without crossover. As mentioned above in Section 2.2, based on the response rate of sotorasib demonstrated in CodeBreaK 100, protocol amendments to CodeBreaK 200 were discussed to mitigate potential issues of open-label bias (see revisions to the SAP in Table 4 below).

Based on Protocol Amendment 3 (February 15, 2021), the efficacy analyses of the primary and key secondary endpoints to compare sotorasib versus docetaxel were conducted on the full analysis set (FAS; intention-to-treat [ITT] population) of CodeBreaK 200. The sample size calculation assumed 90% power to detect a 2.7-month improvement in median PFS (corresponding to a HR of 0.65) with a type I error rate of 2.5% (1-sided). Given these parameters, the required sample size was 330 patients with approximately 230 PFS events required for the final analysis. One interim analysis for PFS was planned when an information fraction of approximately 70% (160 events) of the targeted PFS events was 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. A graphical approach to control Type I error was employed for testing the endpoints of PFS, ORR, OS, and PRO endpoints. The testing procedure specified that ORR and OS would each be tested if PFS were significant, with a proportion of the allocated Type I error of PFS being recycled to each endpoint, and PRO endpoints would be tested only if PFS, ORR and OS were all significant.

Table 4: Revisions to Statistical Analysis Plan

	Original SAP	Revised SAP
Patients randomized (1:1)	650	330
Crossover	No	Yes
Primary endpoint	PFS (BICR)	PFS (BICR)
PFS Statistical Assumptions	230 PFS events HR 0.65 90% power at 1-sided α = 0.025	230 PFS events HR 0.65 90% power at 1-sided α = 0.025
Additional endpoints	OS, ORR (BICR), PROs	OS, ORR (BICR), PROs

Source: FDA review.

3.3 Efficacy Analyses

The analysis of the efficacy results is based on the ITT population which consists of 171 patients randomized to the sotorasib arm and 174 patients randomized to the docetaxel arm. The interim analysis of PFS did not meet the O'Brien-Fleming spending boundary calculated based on 171 number of events observed at the time of the analysis (DCO date: October 5, 2021). After this formal interim analysis, another ad-hoc interim analysis was performed based on updated data for 12 patients in the docetaxel arm and 1 patient in the sotorasib arm. The independent data monitoring committee (iDMC) reviewed both results and recommended continuing the trial without stopping and to perform a global re-reading of scans for the final PFS analysis. The final analysis of the primary and secondary endpoints occurred when 223 PFS events were reached. This analysis of PFS was based on a global re-read of the radiographic images. By the DCO date of this analysis (August 2, 2022), OS had also reached the full maturity (i.e., 100% information fraction) with a total of 203 deaths. Therefore, there will be no further formal OS analyses. At the time of this analysis 46 patients treated with docetaxel with progressive disease (PD) per investigator have crossed over to receive sotorasib.

3.3.1 Baseline Demographics and Key Baseline Characteristics

The patients in CodeBreaK 200 were generally well-balanced between trial arms in terms of patient demographics (Table 5). Baseline characteristics were also generally well-balanced between the two treatment arms, except with regards to PD-L1 expression (Table 6). More patients in the sotorasib arm had PD-L1 protein expression ≥50% compared to patients in the docetaxel arm (35% vs 23%), while fewer patients in the sotorasib arm had PD-L1 protein expression of 1% to 49% compared to patients in the docetaxel arm (27% vs 40%).

Table 5: Patient Demographics for CodeBreaK 200

	Sotorasib N = 171 n (%)	Docetaxel N = 174 n (%)
Age, median (range)	64 (32-88)	64 (35-87)
Age group		
<65 years	91 (53)	95 (55)
≥65 and <75 years	58 (34)	58 (33)
≥75 years	22 (13)	21 (12)
Sex		
Male	109 (64)	95 (55)
Female	62 (36)	79 (45)
Race*		
White	142 (83)	144 (83)
Asian	21 (12)	22 (13)
Black	2 (1.2)	0
Other / Unknown	6 (3.5)	8 (4.5)
Region of enrollment		
North America	20 (12)	22 (13)
Europe	126 (74)	126 (72)
Rest of the world	25 (15)	26 (15)

* Stratification factor
DCO Date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

Table 6: Patient Baseline Characteristics for CodeBreaK 200

	Sotorasib N = 171 n (%)	Docetaxel N = 174 n (%)
ECOG Performance Status		
0	59 (35)	59 (34)
1	112 (66)	115 (66)
Number of prior lines of therapy*		
1	77 (45)	78 (45)
2	65 (38)	69 (40)
>2	29 (17)	27 (16)
Immediately prior line of therapy		
Platinum-based chemotherapy regimen	44 (26)	35 (20)
Non-platinum-based chemotherapy regimen	13 (8)	10 (6)
Immunotherapy with platinum-based chemotherapy	64 (37)	69 (40)
Immunotherapy alone	43 (25)	53 (31)
Other	7 (4.0)	7 (4.1)
History of CNS involvement*		
Yes	58 (34)	60 (35)
No	113 (66)	114 (66)
Smoking status		
Never	5 (2.9)	8 (4.6)
Current	32 (19)	35 (20)
Former	134 (78)	131 (75)
PD-L1 protein expression		
<1%	57 (33)	55 (32)
1% to 49%	46 (27)	70 (40)
≥50%	60 (35)	40 (23)

* Stratification factor
DCO Date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

3.3.2 Patient Disposition

The full analysis set included all randomized patients (N=345 patients [171 sotorasib, 174 docetaxel]). As specified in the SAP, patients who were randomized but did not receive treatment were included in the efficacy summary based on the ITT population. FDA notes the imbalance in early dropout with 23 patients randomized to the docetaxel arm who were never dosed compared to only 2 patients on the sotorasib arm who were randomized but never dosed (see Table 7 below). See Section 4.1 for further discussion regarding the observed asymmetric early dropouts.

Table 7: Patient Disposition for CodeBreaK 200

Disposition	Sotorasib N = 171 n (%)	Docetaxel N = 174 n (%)
Patients randomized but not dosed	**2 (1.2)**	**23 (13)**
Patient request / withdrawal of consent	1 (0.6)	20 (11)
Adverse event	1 (0.6)	0
PI decision	0	1 (0.6)
Disease progression	0	1 (0.6)
Lost to follow-up	0	1 (0.6)
Patients who received at least one dose	**169 (99)**	**151 (87)**
Patients who completed study therapy	0	1 (0.6)
Patients continuing study therapy	22 (13)	7 (4.0)
Patients who discontinued study therapy	147 (86)	143 (82)
Disease progression	103 (60)	95 (55)
Adverse event	29 (17)	25 (14)
Patient request / withdrawal of consent	6 (3.5)	12 (7)
Death	4 (2.3)	6 (3.4)
PI decision / no or loss of clinical benefit	2 (1.2)	5 (2.9)
Decision by Applicant	1 (0.6)	0
Other	2 (1.2)	0

DCO Date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

3.3.3 CodeBreaK 200 Progression-Free Survival (Primary Endpoint)

The primary PFS analysis demonstrated a statistically significant HR of 0.66 (95% CI: 0.51, 0.86) with a median PFS benefit of approximately 5 weeks compared to docetaxel. The clinical significance of the 5-week difference in median PFS, in the absence of OS benefit, is uncertain. The event rate was higher in the sotorasib arm (71% vs 58%). The

primary efficacy results for PFS as assessed by BICR are shown in Table 8 below:

Table 8: Summary of Primary PFS Results as Assessed by BICR for CodeBreaK 200

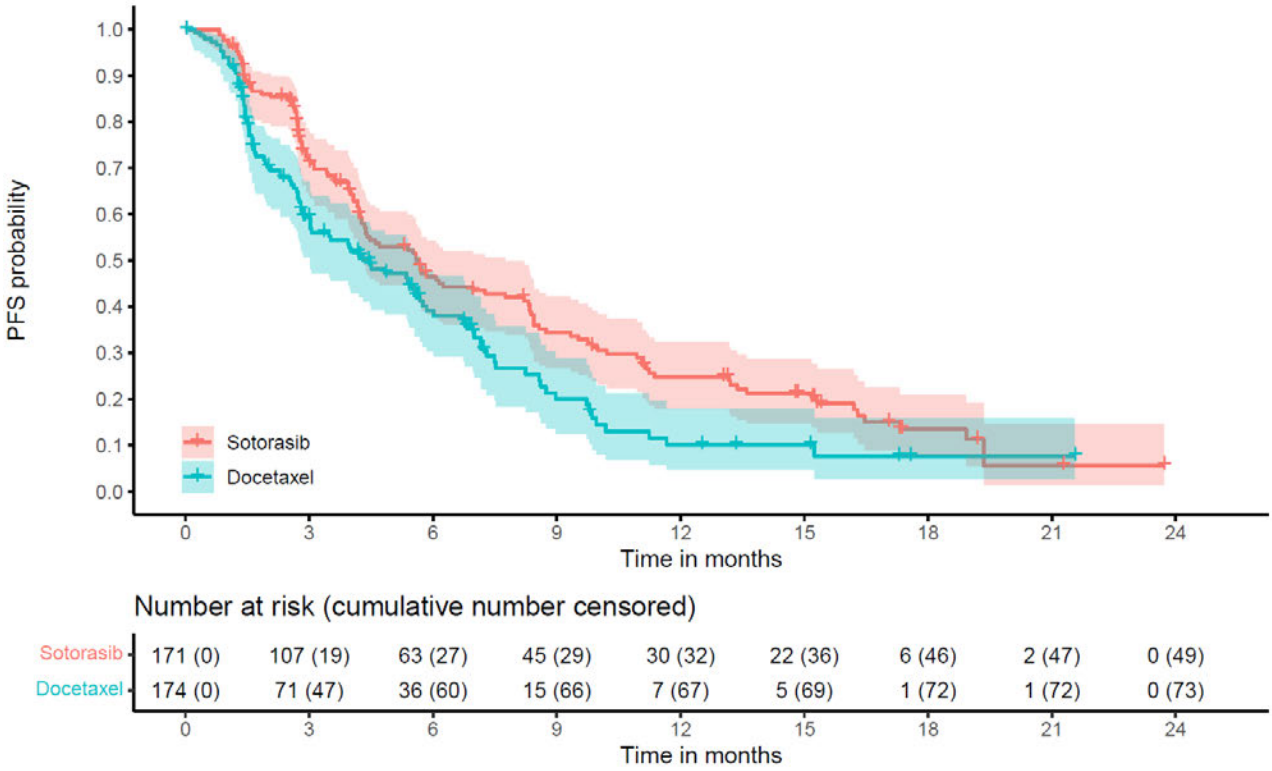
	Sotorasib N = 171	Docetaxel N = 174
Median PFS per BICR, months (95% CI)	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)
PFS events, n (%)	122 (71)	101 (58)
HR (95% CI)	0.66 (0.51, 0.86)	
p-value	0.002	

DCO Date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

The observed PFS HRs were consistent across subgroups, as shown in Figure 6 of the Applicant's Briefing Document.

The PFS Kaplan-Meier curves (Figure 3) demonstrate a modest initial separation between treatment arms that waned until about 7 months of follow-up. After 7 months, there is greater separation, but only a limited number of patients remaining in follow-up, which reduces the reliability of the estimated survival probability. The confidence bands included in the Kaplan-Meier plot of the survival curves illustrate the amount of uncertainty in the estimated PFS over the follow-up time.

Figure 3: Kaplan-Meier Curve for PFS by BICR for CodeBreaK 200



Source: FDA review based on datasets submitted in NDA 214665 s005. DCO: August 02, 2022.

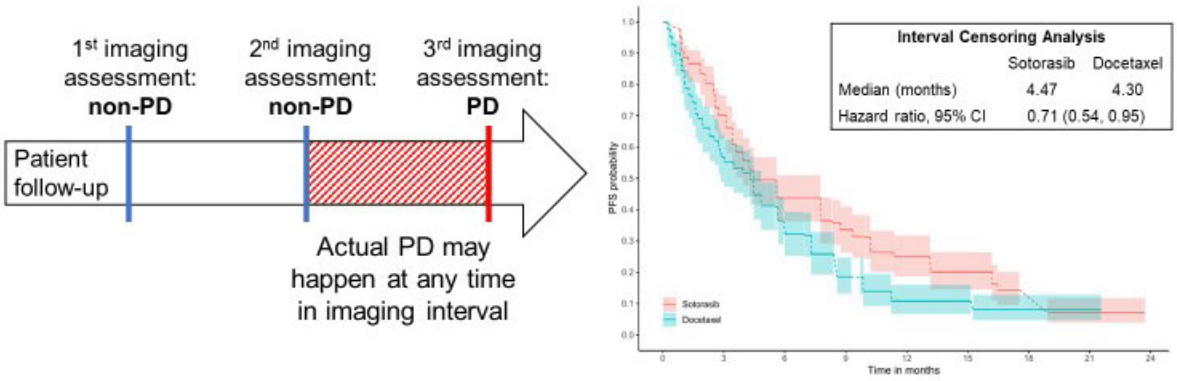
3.3.3.1 Accounting for PFS Assessment Interval

Tumor assessments for patients enrolled in CodeBreaK 200 were made at prespecified intervals corresponding to regularly scheduled visits. Per the protocol, these assessments occurred every 6 weeks for the first 49 weeks, and then every 9 weeks thereafter. As a result, the exact date of disease progression is unknown, but could be assumed to have occurred in the interval between the dates of tumor scans (Figure 4). Although such periodic ascertainment of events may lead to an overestimation of PFS, this approach is considered acceptable since the expected error in measurement should be similar between randomized arms. However, since the median PFS difference of 5 weeks was less than the scan interval of 6 weeks, the results are considered unreliable as it cannot be ruled out that the difference is not due to inherent measurement error. In an open label trial, this is particularly concerning, as there may be additional bias in tumor assessments.

FDA performed an analysis of PFS using interval censoring to investigate robustness of the estimated treatment effect accounting for measurement error in timing of tumor

progression assessments (Figure 4). This analysis is an alternative approach to the primary analysis and assumes that for any patient with an assessment of progressive disease at the end of an assessment interval, their event may have occurred at any time during the imaging interval. The estimated median PFS results from this analysis were 4.2 months (95% CI: 3.9, 7.8) for the sotorasib arm and 4.3 months (95% CI: 2.9, 4.8) for the docetaxel arm with an estimated HR of 0.71 (95% CI: 0.54, 0.95). While the hazard ratio estimate from this sensitivity analysis is relatively consistent with the primary analysis result, the estimated difference in medians is approximately 5 days, which further adds to the uncertainty in the magnitude of PFS difference between treatment arms.

Figure 4: Interval Censored Analysis of PFS by BICR



Source: FDA analysis based on datasets submitted in NDA 214665 s005

3.3.3.2 Robustness of the PFS Primary Endpoint

The Applicant indicates in their Briefing Document that the PFS advantage seen with sotorasib vs docetaxel is consistent across multiple sensitivity analyses, confirming the robustness of the primary endpoint. The Applicant's Briefing Document appears to rely on the consistency of the estimated PFS HR across analyses to assert that the PFS results are robust.

FDA agrees the estimated HR is generally consistent across multiple analyses conducted by the Applicant. However as shown in Section 4.4 of the FDA Briefing Document, the 'statistical significance' of the estimated HR may not hold under different assumptions regarding the level of informative censoring caused by early dropouts and crossover before BICR confirmation of progression.

Furthermore, a complete and balanced assessment of treatment effect on PFS must also include evaluation of the event rates, the shape of the Kaplan-Meier curves, and estimates of median PFS, in addition to the HR. Each of these measures of efficacy for

a time-to-event endpoint play an important role in FDA's assessment of treatment effect. Event rates provide high-level efficacy information and could flag a potentially concerning pattern with safety. Kaplan-Meier curves, which can be presented with confidence bands to provide an understanding of the variability in estimation, provide a comprehensive picture of survival follow-up. These curves provide context in the estimation of summary measures, such as the hazard ratio and medians, as the apparent separation or convergence of curves must be considered along with treatment effect estimates.

The summary measures generally considered for time-to-event endpoints, hazard ratios and median PFS, are helpful in providing quantitative estimates of treatment effect. The hazard ratio can be informative for assessing overall risk reduction when certain assumptions are met. Medians encapsulate expected survival experience of an average patient, utilizing follow-up information from patients enrolled on the trial. A given hazard ratio could mean different magnitude of benefit in terms of prolongation of time to progression, and medians contextualize the clinical meaningfulness of relative treatment effect estimated using hazard ratio. Therefore, FDA considers both hazard ratio and median along with event rates and the overall Kaplan-Meier curves when assessing benefit of an investigational treatment.

As further detailed above in Section 3.3.3.1 of the FDA Briefing Document and Section 5.1.11.5 of the Applicant’s Briefing Document, the median PFS benefit of sotorasib vs docetaxel may be as low as 5 days based on an additional analysis using an interval censoring method. This minimal median PFS benefit may call into question the robustness of the PFS benefit of sotorasib and our ability to quantify the treatment effect.

3.3.3.3 Interpretation of the PFS Results

Given the subjective nature of PFS as an endpoint, outcome assessments can vary across different assessors. Therefore, it is critically important in measuring efficacy that the magnitude of investigational treatment effect on PFS be large enough to overcome potential sources of variability. Interpretation of these PFS results is further complicated by various sources of potential bias due to the open-label nature of the trial (discussed in Sections 4.1 – 4.3 below). There is a high uncertainty in the magnitude of PFS benefit of sotorasib over docetaxel, due to the marginal treatment effect on PFS and potential bias observed in the trial:

- The observed improvement in median PFS (i.e., 5 weeks) is less than the 6-week imaging interval. There is inherent measurement error in PFS due to the disease assessments occurring at the end of the imaging interval even though actual progression may occur at any time during the interval (i.e., interval censoring). As

a result, the true median PFS benefit may be less than 5 weeks and as small as 5 days. (Section 3.3.3.1)

- There were asymmetric early dropouts with 23 (13%) of 174 patients randomized to docetaxel compared to 2 (1%) of 171 patients randomized to sotorasib who did not receive any study therapy. This large imbalance of untreated patients is not only a potential indication of systemic bias but is also a source of bias impacting the estimation of the treatment effect. As the patients who withdrew consent immediately after randomization were censored at that time and provided very little information relevant to the determination of the treatment effect, it is unknown to what extent the PFS treatment effect would have changed, and in what direction, had the patients stayed in the trial. (Section 4.1)
- Investigator-based assessments of PFS favored sotorasib. There were greater early calls of PFS by investigators compared to BICR assessment for the docetaxel arm (early discordance). There were more late calls of PFS by investigators compared to BICR assessments for the sotorasib arm (late discordance). (Section 4.2)
- There was early crossover to sotorasib treatment of patients in the docetaxel arm before BICR-assessed progressive disease. When a patient is determined to have PD by an investigator and is initiated on subsequent anti-cancer therapy, BICR assessment of progression is confounded by interference of the new therapy. (Section 4.3)
- There was lack of adherence to the imaging charter and protocol, involving multiple BICR assessments of the PFS primary endpoint. This protocol deviation erodes confidence in the overall trial conduct and data integrity. (Section 4.6)

Given these trial design and conduct issues, FDA is concerned CodeBreaK 200 may not be considered an adequate and well-controlled trial and therefore may not provide substantial evidence to support the claims of effectiveness of sotorasib. Adequate measures were either not put in place, or not adequately followed to minimize bias on the part of investigators, analysts, and likely patients as well.

3.3.4 Overall Survival

The primary analysis results of OS failed to demonstrate a survival advantage of sotorasib over docetaxel. The OS HR at the time of the primary analysis was 1.01 (95% CI: 0.77, 1.33) with a median OS of 10.6 months (95% CI: 8.9, 14.0) in the sotorasib arm and 11.3 months (95% CI: 9.0, 14.9) in the docetaxel arm. Additional data from the 90-day safety update resulted in an OS HR of 0.96 (95% CI: 0.74, 1.24) with similar medians as the primary analysis. In total, 46 (26%) patients crossed over from the docetaxel arm to receive sotorasib treatment. The Applicant indicates in their Briefing Document that all 46 patients crossed over after centrally-confirmed progressive

disease. FDA notes that while scans for all 46 patients that were assessed by investigators to have progressive disease were reviewed by the independent COP radiologist before crossover, 19 of these patients did not have BICR confirmation of progressive disease before crossover to sotorasib treatment. See Section 4.3 for additional details.

A summary of the OS results at the time of the primary analysis is shown in Table 9 below.

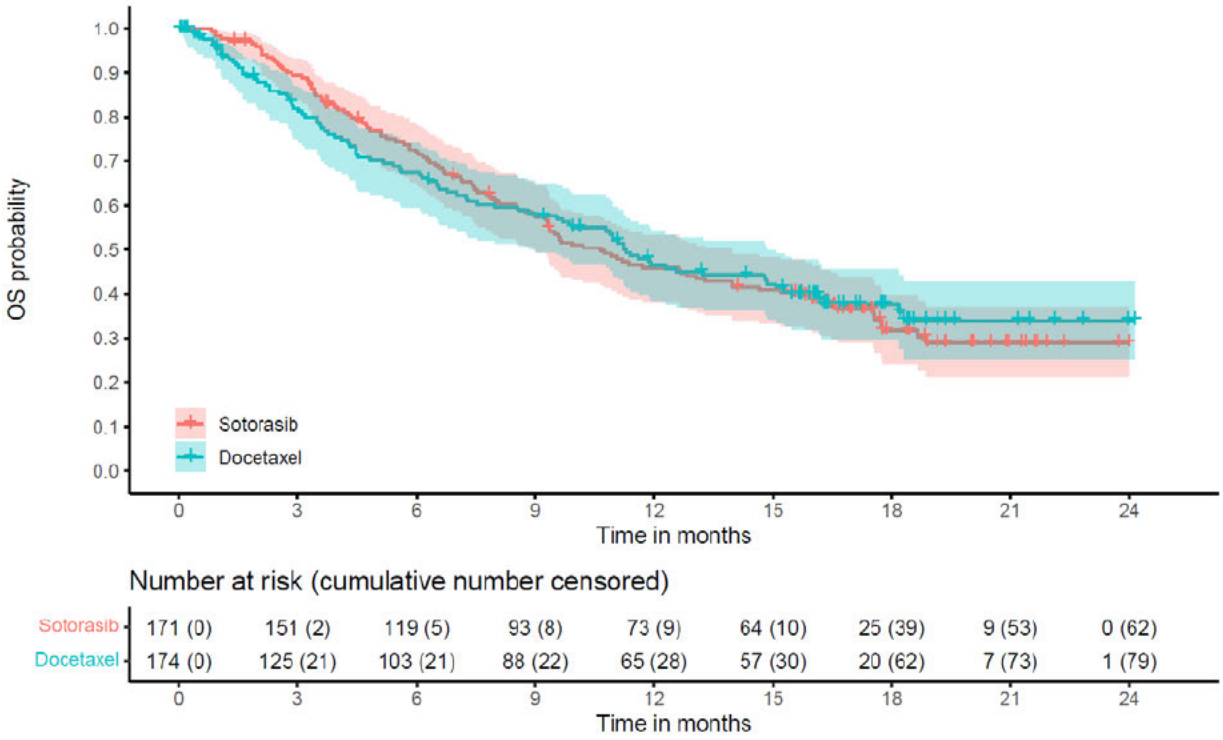
Table 9: Summary of OS Results for CodeBreaK 200

	Sotorasib N = 171	**Docetaxel N = 174**
Median OS, months (95% CI)	10.6 (8.9, 14.0)	11.3, (9.0, 14.9)
Deaths, n (%)	109 (64)	94 (54)
HR (95% CI)	1.01 (0.77, 1.33)	
p-value	0.53	
Crossover from docetaxel to sotorasib, n (%)	46 (26%)	

DCO Date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

The OS Kaplan-Meier curve at the time of the primary analysis is shown below in Figure 5. The plot indicates that over the entire follow-up period, there is no separation between the curves for those patients randomized to sotorasib and those patients randomized to docetaxel, suggesting a lack of survival benefit. In CodeBreaK 200, OS is not improved with sotorasib treatment compared to docetaxel and the results do not definitively rule out potential detriment.

Figure 5: Kaplan-Meier Curve for OS for CodeBreaK 200



Source: FDA review based on datasets submitted in NDA 214665 s005. DCO: August 2, 2022.

3.3.5 Additional Endpoints

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

Sotorasib demonstrated a statistically significant improvement in ORR over docetaxel as summarized in Table 10 below.

Table 10: Summary of ORR Results as Assessed by BICR for CodeBreaK 200

	Sotorasib N = 171	Docetaxel N = 174
ORR per BICR, % (95% CI)	28 (22, 35)	13 (9, 19)
Odds ratio (95% CI)	2.60 (1.48, 4.56)	
p-value	<0.001	
Median DOR, months (range)	8.6 (6.9, 12.3)	6.8 (4.3, 8.3)

DCO Date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

The ORR results in CodeBreaK 200 are similar to the ORR of 36% (95% CI: 28, 45) previously reported in CodeBreaK 100.

3.3.5.2 Patient Reported Outcomes

Patient reported outcomes (PROs) were collected at each 21-day cycle. The PRO instruments and items collected EORTC QLQ-C30, the lung cancer specific module of EORTC QLQ-LC13, PRO-CTCAE, BPI-SF, and the GP5 item of FACT-G.

For evaluation of clinical benefit, change from baseline to Week 12 (cycle 5 day 1) were planned to be formally tested in the following PRO-based endpoints: dyspnea (4-item domain from QLQ-LC13 and QLQ-C30), cough (QLQ-LC13), chest pain (QLQ-LC13), physical functioning (QLQ-C30), and global health status (QLQ-C30). In general, global health status is subject to confounding by non-treatment/non-disease factors. FDA generally focuses on PRO concepts that are proximal to the disease and treatment being studied, as outlined in the FDA draft guidance on core PROs in cancer clinical trials (Draft Guidance: Core Patient-Reported Outcomes in Cancer Clinical Trials).

Since OS was not statistically significant, statistical testing of efficacy endpoints stopped. Therefore, the PRO-based endpoints were not formally tested and are considered exploratory only. However, for descriptive comparisons between treatment arms, completion rates were evaluated based on all randomized patients as a fixed denominator. Completion rates from baseline to cycle 5 ranged from 62% to 98% in the sotorasib arm and 40% to 91% in the docetaxel arm. The lower completion rates were a result of only collecting PRO assessments from patients who were still on treatment and expected to complete PRO assessments.

Additionally, the mixed effect model for repeated measures (MMRM), which is the pre-specified analysis method for the PRO-based endpoints, relies on the assumption that data for patients who did not complete the PRO assessment are missing at random where. In other words, patients with missing assessments were assumed to behave similarly to patients still on treatment. The validity of the missing at random assumption is questionable given early dropouts on the control arm and other evidence of systemic bias in this open-label trial. Therefore, the differential completion rates make interpretation of PRO-based endpoints difficult from a clinical benefit perspective as there may be potential bias in the estimation of treatment effects. Clinical meaningfulness from a patient perspective was not formally assessed as it is generally only evaluated in the context of interpreting PRO-based endpoints that were reliably estimated for clinical benefit.

For evaluation of safety and tolerability, FDA considered PROs such as global side effect bother (GP5 item of FACT-G), diarrhea (EORTC QLQ-C30), and patient-reported symptoms selected from PRO-CTCAE in the first six months of treatment. Compliance rates, defined as the percentage of patients completing the PRO assessment where

that assessment is expected to be given was generally high over 90%. A total of 73 (43%) patients and 34 (20%) patients were still eligible and were expected to complete PROs at cycle 8. Among patients who completed the GP5 item for side effect bother, the percentage of patients who reported having some level of side effect bother ranged from 30%-41% in the sotorasib arm and 62%-75% in the docetaxel arm in the first 8 cycles of treatment.

3.4 Safety Results

The safety analysis of sotorasib versus docetaxel is based upon the safety analysis set (SAS), which includes all patients in the FAS who received at least one dose of investigational product. The SAS includes 169 patients on the sotorasib arm and 151 patients on the docetaxel arm.

Table 11 summarizes the overall safety profile of sotorasib compared to docetaxel.

Table 11: Summary of Safety Results for CodeBreaK 200

	Sotorasib N = 169 n (%)	Docetaxel N = 151 n (%)
All-cause treatment-emergent adverse events (TEAEs)		
Any grade	138 (82)	139 (92)
Grade ≥ 3	94 (56)	84 (56)
Fatal TEAEs	11 (7)	11 (7)
Serious TEAEs	64 (38)	60 (40)
TEAEs leading to discontinuation	22 (13)	22 (15)
TEAEs leading to dose reduction	26 (15)	42 (28)
TEAEs leading to dose interruption	83 (49)	40 (26)

DCO Date: August 2, 2022
Source: FDA review based on datasets submitted in NDA 214665 s005

At the time of the primary analysis, 64% (n=109/171) of patients had died on the sotorasib arm compared to 54% (n=94/174) of patients on the docetaxel arm in the efficacy population. However, the death rates were more similar when only evaluating patients who had received at least one dose of study therapy (i.e., the safety population), at 63% (n=107/169) for sotorasib versus 59% (n=89/151) for docetaxel. Additional data from the 90-day safety update revealed even more similar death rates for sotorasib and docetaxel for both the efficacy and safety populations. There were also equal rates of fatal TEAEs (7%) for both treatment arms.

The Applicant presents additional safety data in the Applicant Briefing Document.

Overall, no new safety signals were identified for sotorasib in CodeBreaK 200.

4. INVESTIGATION OF POTENTIAL SOURCES OF BIAS

As CodeBreaK 200 is an open-label trial, it is subject to systemic bias due to knowledge of treatment assignment, particularly as docetaxel is known to have a historically poor response rate for the second-line treatment of patients with NSCLC. This type of bias occurs when knowledge of treatment assignment can influence patient and investigator attitude, behavior, and decisions as they relate to treatment adherence and trial-related activities, such as patient management and disease assessment. Bias can also permeate to other aspects of trial conduct including adverse event reporting and patient reported outcomes. In this trial, there are indications of patient preference for investigational treatment, investigators' preference for sotorasib, and some degree of interference with the initial BICR process. Each of the indicators described below not only signal systemic bias and related study conduct issues, but also impact the statistical integrity of the time-to-event analysis undertaken to estimate the treatment effect. Such bias would be concerning in any trial, but in CodeBreaK 200 this concern is compounded by the marginal efficacy results. The potential systemic bias in CodeBreaK 200 may be difficult to overcome to reliably determine superiority of sotorasib over docetaxel, given the marginal PFS benefit and no difference in OS.

4.1 Early Dropouts in the Docetaxel Arm

4.1.1 Potential Indication of Systemic Bias

CodeBreaK 200 was designed to randomize patients 1:1 to sotorasib, an experimental treatment which had never been studied in a randomized controlled trial, or docetaxel, a standard of care therapy in the second line setting for patients with NSCLC. However, there was developing enthusiasm in the oncology community for sotorasib and docetaxel was known to have a historically marginal response rate. This apparent preference for sotorasib over docetaxel treatment is reflected in the patient disposition data, which exhibits an imbalance in important patient attrition rates across trial arms

Only 2 (1%) of the 171 patients randomized to the sotorasib arm of CodeBreaK 200 did not initiate treatment, whereas 23 (13%) of 174 patients randomized to the docetaxel arm did not initiate treatment (see Table 7). These 23 patients were not concentrated at specific trial sites, as they were enrolled at 18 different sites under different investigators. Additionally, 20 patients on the docetaxel arm withdrew consent within 5 weeks after randomization (18 of these patients refused treatment and are included in the 23 patients who were randomized to but did not receive treatment on the docetaxel arm), compared to no such early withdrawals on the sotorasib arm.

4.1.2 Impact on Estimation of the PFS Treatment Effect

The large imbalance of untreated patients and withdrawals of consent across arms not only are an indication of systemic bias in the conduct of CodeBreaK 200, but also are a source of bias impacting the estimation of the treatment effect. Specifically, patients who withdrew consent immediately after randomization no longer contributed information to the trial follow-up data. The loss of this patient level information generally results in a loss of randomization; in other words, the balance of important known and unknown prognostic variables across treatment arms achieved by randomization may be lost when a large number of patients dropout, particularly if the dropout is predominantly on one arm. As a result, if patients on the control arm who withdrew consent have better prognoses than those patients who remained on trial, the treatment effect of sotorasib compared to docetaxel would have been overestimated.

Analyses were performed to compare the baseline demographics of patients who withdrew from the trial early to patients who remained on trial, to evaluate for the presence of potential differences. While there were some characteristics that were similar between patients who withdrew consent and those who remained on the docetaxel arm, the patients who withdrew consent had a slightly higher rate of liver metastasis, a higher rate of PD-L1 negative tumors (<1%), and lower current smoking status. When examining outcomes, the patients on the docetaxel arm with liver metastasis seemed to perform poorly, while those who are not current smokers or with PD-L1 expression <1% seemed to have relatively longer PFS. These descriptive comparisons should be interpreted with caution as they are based on a small number of patients who dropped out and do not provide a reliable assessment of similarity or difference between the two groups of patients.

As the patients who withdrew consent immediately after randomization were censored at that time and provided very little information relevant to the determination of the treatment effect, it is unknown to what extent the treatment effect would have changed, and in what direction, had the patients stayed in the trial. While statistical techniques may adjust for known prognostic factors, these techniques are unable to adjust for the influence of unmeasured factors that tend to indirectly impact outcome, such as socioeconomic status, patient knowledge or awareness of treatment options, and patient will and purpose for living[19].

4.1.3 Sensitivity Analyses of PFS to Investigate Impact of Early Withdrawal

Based on the substantial difference in early withdrawal between trial arms, it is unclear how this difference contributed to the observed results of the trial. FDA therefore

performed stress test analyses to assess if the sotorasib advantage over docetaxel observed in the primary PFS analysis persists, under a set of plausible assumptions about early censoring.

In the sensitivity analyses shown in Table 12, FDA imputed PFS time for the 20 patients in the docetaxel arm who were censored on day 1 for having no post-baseline assessment. In the multiple imputations, the PFS times for the 20 patients without post-baseline assessment were sampled from the top 50% best PFS times observed (based on Kaplan-Meier estimation to account for censoring) either in all patients (multiple imputation 1) or in patients from the docetaxel arm only (multiple imputation 2). The results suggest that if the 20 patients (censored on day 1) were assumed to have a similar PFS as that of the top 50% patients with the longest PFS in the trial, the 95% confidence interval of the estimated HR will include 1. This then, would not rule out the possibility that the observed difference in PFS is due to a chance.

In the tipping point analysis, the 20 patients without post-baseline assessments were assumed to have a reduced risk compared to those still in follow-up. A grid search algorithm was used to find the minimal percentage reduction needed (in an increment of 5%) such that the 95% confidence interval will include 1. If OS is known, the imputed time is restricted to be shorter than the OS time. The results suggest that if the 20 patients (censored on day 1) were assumed to have at least 55% lower risk of progression compared to those still in follow-up, the 95% confidence interval of the estimated HR will include 1. This then, also would not rule out the possibility that the observed difference in PFS is due to a chance.

Table 12: Sensitivity Analyses of PFS to Investigate Impact of Early Withdrawal

Sensitivity Analyses of PFS per BICR	PFS assumption for imputation	HR (95% CI)
Primary analysis per protocol	N/A	0.66 (0.51, 0.86)
PFS Multiple imputation 1	PFS times sampled from 50% best PFS times in both arms (mPFS = 9.9 months)	0.77 (0.58, 1.01)
PFS Multiple imputation 2	PFS times sampled from 50% best PFS times in docetaxel arm (mPFS = 8.1 months)	0.73 (0.56, 0.96)
PFS Tipping point analysis 1	Risk of event 55% lower than other patients in docetaxel arm	0.76 (0.57, 1.01)

Source: FDA analysis based on datasets submitted in NDA 214665 s005

4.2 Investigator Assessment of PFS

The potential for bias in investigator-based assessment of progression assessments in open-label trials is well described[20,21]. In the case of CodeBreaK 200, it is conceivable that investigator enthusiasm for sotorasib compared with docetaxel could result in a higher rate of premature assessments of progression on the docetaxel arm as well as delayed determination of progression on the sotorasib arm.

To minimize such early calls, the Applicant instituted an independent COP process to obtain a second opinion on the investigators' progression calls. All COP reviews were triggered by investigator determination of radiographic progression. See Section 3.1 for additional details about the COP procedure.

To assess potential bias in site investigators' evaluation of disease progression, FDA investigated discordance between investigator and BICR assessment of disease progression. FDA analysis focused on differences in the timing of an assessment of progressive disease in patients who were determined to have progression by either or both assessors. FDA considered early discordance to be when investigator assessment of progressive disease occurred earlier than BICR determination of progression. Conversely, FDA considered late discordance to be when investigator assessment of progressive disease occurred later than BICR determination of progression.

It is expected that in most oncology trials, some discordances between investigators and BICR assessment of PFS will occur due to random variation. However, in the absence of bias, the distribution of overall discordance, as well as types of discordance (early versus late), should be equal across arms. A substantial difference in the distribution of rate and/or type of discordance between treatment arms, such as those

described for CodeBreaK 200 in Table 13, is an indication of potential bias in the investigator's disease assessment due to knowledge of treatment assignment.

Table 13: Discordant Progression Calls between Investigator and BICR Assessments

Type of Discordance	Sotorasib n = 89		Docetaxel n = 67
Early Calls by Investigator	52 (58%)	vs	46 (69%)
Late Calls by Investigator	37 (42%)	vs	21 (31%)

Patients with BICR censored before investigator calls, or patients with investigator censored before BICR calls were excluded from the analysis; differences in progression call times by ≤ 3 days were considered concordant; prespecified censoring rules were applied before the analysis.
Source: FDA analysis based on datasets submitted in NDA 214665 s005

When early discordances are higher in the docetaxel arm compared to the sotorasib arm (and a corresponding greater proportion of later discordances are on the sotorasib arm compared to the docetaxel arm), as shown above (Table 13), this indicates either that (1) investigators were more likely to take patients off docetaxel earlier than they were to take patients off sotorasib or (2) they were more likely to keep patients on sotorasib longer than to keep patients on docetaxel or (3) some combination of both. These types of biases indicate investigator's preference for sotorasib.

4.3 Crossover Before Progressive Disease per Blinded Independent Central Review

4.3.1 Potential Indication of Systemic Bias

A related concern to the observed early discordance in progressive disease assessment is the early crossover to sotorasib treatment of patients in the docetaxel arm. Early crossover is defined as patients crossing over based on investigator-assessed progressive disease (PD), prior to BICR-assessed PD. When a patient is determined to have PD by an investigator and is initiated on subsequent anti-cancer therapy, BICR assessment of progression is confounded by interference of the new therapy. These patients are then censored at the last assessment time prior to new therapy, which leads to incomplete information for the assessment of PFS per BICR. Incomplete information for the assessment of PFS per BICR is particularly concerning as this is the primary endpoint of CodeBreaK 200.

Disproportionate censoring due to new anti-cancer therapy with higher rates of censoring on the docetaxel arm, including for patients who crossover to sotorasib treatment, is further indication of systemic bias favoring the sotorasib arm.

4.3.2 Impact on Estimation of the PFS Treatment Effect

Crossover before progressive disease per BICR manifests as statistical bias, as the missing primary outcome assessment for these patients due to censoring will bias the estimation of the primary PFS endpoint. Of specific concern is the possibility that the patients who crossed over to receive sotorasib treatment are healthier and have a better prognosis and outcomes than those who did not crossover after progression. In this case, the censored BICR disease assessments for these patients would likely be missing data that would have been otherwise indicative of a longer patient-level PFS, benefiting the docetaxel arm.

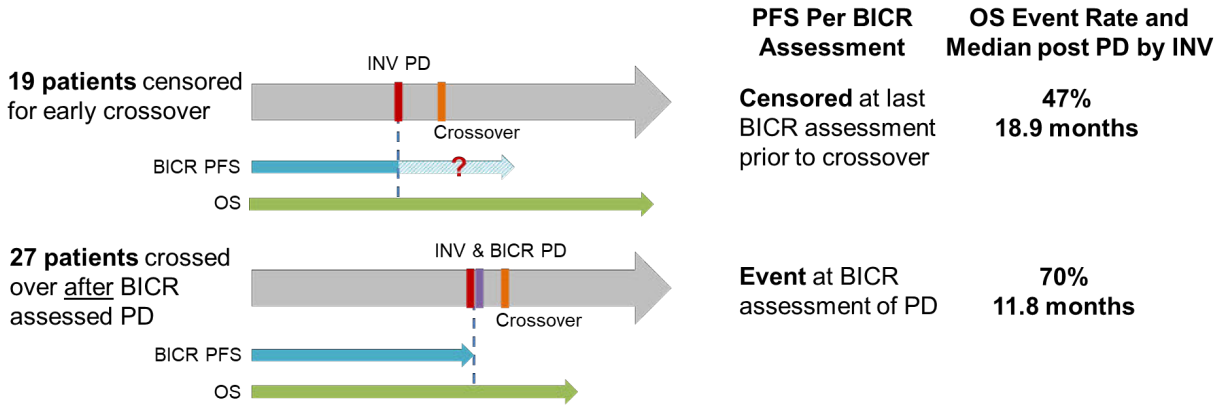
Of the 46 patients on the control arm of CodeBreaK 200 who crossed over to sotorasib, 19 patients crossed over early (i.e., they did so following investigator-assessed disease progression but before BICR-assessed disease progression). As described above, their radiologic scans were censored at the last BICR assessment. To understand whether these patients are prognostically different than those patients in the docetaxel arm who have not crossed over prior to BICR assessment of progressive disease, FDA compared outcomes across these two groups of patients on the control arm, depicted in Figure 6.

Since those patients who crossover prior to BICR-assessed progressive disease have censored BICR PFS assessments, FDA compared OS of the 19 patients who crossed-over before BICR-assessed progressive disease (patients with “early crossover”) to the 27 patients who crossed-over to sotorasib after assessment of progressive disease by both investigator and BICR. In the 19 patients with early crossover, the median OS was 24.4 months with 9 (47%) deaths. In comparison, the median OS for the 27 patients who crossed over after progressive disease assessment by both investigator and BICR was 16.2 months with 19 (70%) deaths.

To account for the lead time, which in this case is the period from randomization to investigator-assessed progression in which patients could not have an OS event, FDA also analyzed the survival time after investigator-assessed progression. The median post-progression survival was 18.9 months for the 19 patients with early crossover and 11.8 months for the other 27 patients. The post-progression risk of death was 58% lower for the patients who crossed over without progression confirmed by BICR with an unstratified HR of 0.42 (95% CI: 0.19, 0.95). Therefore, it is plausible that the 19 patients with early crossover may have had improved prognoses compared to patients who had crossover after both investigator and BICR assessment of progressive disease.

As both groups of patients were treated with sotorasib after disease progression called by investigators, the difference in OS after investigator assessed progression could not be attributed to the subsequent sotorasib treatment. Although there was a difference of approximately two months between the two groups in the initiation of sotorasib (median time to sotorasib treatment was 4.5 months among the 19 patients with early crossover and 6.5 months among the 27 patients with crossover after investigator and BICR assessment of progressive disease), it is unlikely that this difference is attributable to the estimated 8-month difference in post-crossover survival between the groups.

Figure 6: PFS and OS Follow up in Crossover Patients



Gray arrows indicate patient on-study follow-up, blue arrows indicate the primary endpoint – PFS assessed by BICR, and green arrows indicate overall survival. Single red bar indicates assessment which is determined to be PD by investigator (with COP) only, double bar with red and purple indicates assessment determined to be PD by both investigator (with COP) and BICR, and orange bars indicate patient crossover. At the time of crossover, if the patient has not been determined to be PD by BICR, the PFS by BICR will be censored at the lastest assessment timepoint when the patient is known to have non-PD by BICR.
Source: FDA analysis based on datasets submitted in NDA 214665 s005

As noted above, the patients who crossed over before disease progression per BICR may have lower risk of death and longer OS compared to the remaining 27 patients who crossed over but were not censored for PFS. These results, together with eligibility criteria for crossover, suggest that patients who were willing and eligible to crossover before BICR confirmed progression could have been relatively healthier than those remaining in follow-up in the docetaxel arm. If such is the case, then the observed treatment effect on PFS, which is already small, could be an overestimation of the true treatment effect.

4.4 Impact of Crossover before PD by BICR and Early Dropout on PFS

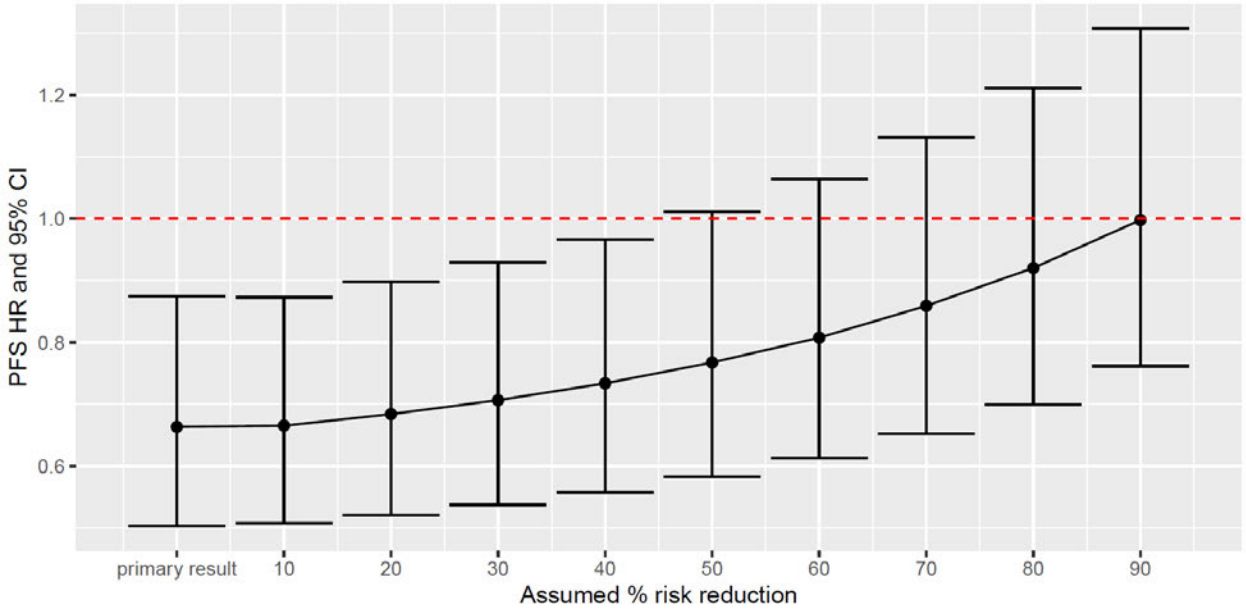
The primary analysis of PFS assumes that the patients who were censored are no more

or less likely to have disease progression than those who were not censored (i.e., assumes non-informative censoring). If the censored patients are considered less frail or are at lesser risk of progression than those who were not censored, the estimated difference in PFS between arms could be reduced further. Therefore, the impact of the potential statistical bias affecting the estimates of PFS due to informative censoring depends on how different the censored patients are than those who were not censored.

As described in Sections 4.1.2 and 4.3.2, there are concerns for informative censoring due to the substantial difference in early withdrawal between trial arms and crossover before PD by BICR. FDA conducted tipping point analysis to assess the combined impact of these two sources of informative censoring on the PFS results of the trial.

In the tipping point analyses, the 19 patients who crossed over and the 20 patients without post-baseline assessments were assumed to have a reduced risk compared to those still in follow-up. A grid search algorithm was used to find the minimal percentage reduction needed (in an increment of 5%) such that the 95% confidence interval will include 1. If OS is known, the imputed time is restricted to be shorter than the OS time. Figure 7 shows a gradual shift in the estimated hazard ratios and corresponding confidence intervals towards 1 (i.e., a result that would not be statistically significant) as mild, moderate, and high levels of stress were applied to the observed data. This was accomplished by varying assumptions regarding risk of progression or death for the patients with incomplete BICR PFS information. The results suggest that if the 20 patients (censored on day 1) and the 19 patients who crossed over were to have at least 50% lower risk of progression compared to those still in follow-up, the 95% confidence interval of the estimated HR will include 1. If this assumption were true, the results would not rule out the possibility that the observed difference in PFS is due to a chance. The estimated HR would also approach 1 if the informative censoring is moderate to severe.

Figure 7: Tipping Point Analysis – Change in Estimated Hazard Ratio with Varying Assumptions for Patients who Withdrew Early or Crossed Over to Sotorasib



Source: FDA analysis based on datasets submitted in NDA 214665 s005.

4.5 Impact of Crossover and Early Dropout on OS

The interpretation of OS is complicated by crossover of patients from the docetaxel arm to sotorasib treatment and informative censoring due to early dropout of patients who were randomized but not treated. These factors have an unknown impact on the observed OS results, with the magnitude, direction, and extent of impact varying depending upon the assumptions made for these patients. Crossover may not only attenuate a treatment benefit but may also conceal a decrement in survival.

As shown in the middle three rows of Table 14, FDA conducted three sensitivity analyses to assess the impact of crossover, including using rank preserving structural failure time model (RPSFTM), inverse probability of censoring weighted analysis (IPCW), and a two-stage model. These analyses used the most mature data from the 90-day safety update, and the results were generally consistent with the primary analysis. Although these results should be interpreted with caution due to strong statistical assumptions, they indicate it is unlikely that crossover to sotorasib for patients on the control arm is attributable for the lack of survival benefit.

FDA also conducted additional sensitivity analyses, including tipping point analyses, to assess the impact of early withdrawal of consent of patients on the control arm (see the last three rows of Table 14). The results of these sensitivity analyses suggest that the hazard ratio estimate could be greater than 1 if the patients who were randomized to docetaxel but not treated were expected to have moderately longer survival than those

patients who remained in the trial. Alternatively, the tipping point analysis indicates that a hazard ratio below 0.9 may be observed if these patients have a doubled risk of death (105%) compared to the patients who remained in the trial. The primary analysis results, and results from the Applicant's and FDA's additional analyses, suggest that strong assumptions regarding patients who crossed over or withdrew early would be required to alter the conclusion that there is no difference in OS between sotorasib and docetaxel.

Table 14: Sensitivity Analyses of OS to Investigate Impact of Crossover and Early Withdrawal

Data issue	Analysis	Description / Key Assumption	HR (95% CI)
N/A	Primary analysis per protocol	Original analyses	1.01 (0.77, 1.33)
	90-Day safety update		0.96 (0.74, 1.24)
Crossover of patients on docetaxel arm to sotorasib	RPSFTM adjusted analysis	Construct counterfactual outcome assuming treatment effect is same for crossover patients	0.96 (0.71, 1.43)
	IPCW adjusted analysis	Adjust for factors associated with crossover, assuming there is no unmeasured confounding factor	1.03 (0.78, 1.37)
	Two-Stage approach		0.95 (0.63, 1.33)
Early withdrawal of 17 patients on control arm within 5 weeks of randomization	Multiple imputation	OS times sampled from 50% best OS times in both arms	1.06 (0.82, 1.38)
	Tipping point analysis (HR ≥ 1.1)	Risk of event 80% lower than those remaining in follow-up	1.10 (0.84, 1.43)
	Tipping point analysis (HR ≤ 0.9)	Risk of event 105% higher than those remaining in follow-up	0.90 (0.70, 1.16)

Source: FDA analysis based on datasets submitted in NDA 214665 s005

4.6 BICR Assessment of PFS and Imaging Vendor Procedures

To assess PFS by BICR, each scan was reviewed by two BICR radiologists. Adjudication would occur at each timepoint if there were a discrepancy in timepoint

response between the two readers on the same patients. In CodeBreaK 200 Protocol Amendment 3, a provision for an independent COP procedure by a single independent radiologist (different from BICR) was added. See Section 3.1 for details about the COP procedure. According to the protocol amendment, the purpose of the COP reading was to provide the site investigators with a second independent opinion regarding whether patients had reached progressive disease according to RECIST v1.1. According to the imaging charter, "the COP will only be utilized to provide a second opinion on the presence or absence of progression at the current time point to the site PI [Principal Investigator] …" This COP service was provided by the same imaging vendor responsible for BICR reads ((b) (4)).

The potential impact of COP on the BICR assessment of progression events is usually minimal if the COP procedure is used as intended. However, there was a lack of adherence to the imaging charter and protocol as the COP assessments were indirectly used to audit the BICR assessments.

The Applicant initially identified a higher-than-expected number of patients (n=51; 15%) being censored for starting new anticancer therapy. Of these 51 patients, 23 patients had COP confirmed progression. Notably, all 23 of these patients were from the docetaxel arm, which appears to be a result of the subgroup evaluated (i.e., patients who were censored for initiation of new anticancer therapy and also had COP review of imaging). The Applicant informed (b) (4) of a higher-than-expected discordance between the COP-based and BICR-based events of progression.

Of these 23 patients, (b) (4) identified unexpected reader variability between COP and BICR assessments for 13 patients. The unexpected reader variability was related to cases of borderline imaging and instances in which the BICR reader may not have fully followed the read rules for imaging assessments. A BICR re-read was selectively performed for these 13 patients.

This resulted in changes in the status of 11 patients in the docetaxel arm who were originally assessed as having non-progressive disease per BICR to progressive disease on the BICR re-read. These changes also resulted in a change for the initial interim analysis PFS results from being statistically not-significant to statistically significant.

The Applicant informed FDA of the above events and inquired whether the updated, statistically significant interim PFS results would be adequate to support a marketing application for sotorasib. During an ad hoc meeting between the Applicant and FDA on May 5, 2022, FDA indicated the results would not support a marketing application and advised for the trial to continue.

A global re-read for the analysis of the primary PFS endpoint was undertaken under the advisement of the iDMC and FDA, given concerns of data quality and in an effort to achieve consistency in BICR reads from a single data reading entity. However, this non-adherence to the prespecified roles of the COP and BICR entities and the fact that

images from only the docetaxel arm were selected for additional review depletes confidence in the overall trial conduct and data integrity.

4.7 Impact of potential systemic bias on other secondary efficacy endpoints

The prior sections discuss the impact of potential systemic bias on the primary endpoint of BICR PFS and the secondary endpoint OS. However, the observed systemic bias is also likely to manifest as statistical bias with respect to the estimation of treatment effect on other secondary endpoints such as ORR. For example, early asymmetric dropouts result in a greater number of patients on the control arm who are considered non-responders due to no post-baseline assessments. If these patients are more likely to have a response, there is bias in the estimation of the response rate.

Formal evaluation of comparative benefit cannot be concluded for the PRO-based endpoints. Estimation of treatment effect based on the MMRM may be misleading since the modeling assumptions are likely implausible in the presence of the intercurrent events observed in this study.

Evaluation of safety and tolerability was performed based on patients who were still on treatment. It is important for the descriptive assessment of PROs to be interpreted in the context of the timing of intercurrent events such as death and disease progression, particularly since they differ between treatment arms. Information on death, disease progression, and treatment discontinuation (including dropout) are important to provide a full picture of the patient experience.

5. SUMMARY AND CONCLUSIONS

On May 28, 2021, sotorasib was granted accelerated approval for the treatment of patients with *KRAS-G12C*-mutated NSCLC, who had received at least one prior systemic therapy. The approval was based on the single-arm trial CodeBreaK 100 which demonstrated an ORR of 36% (95% CI: 28%, 45%), with a corresponding median DOR of 10 months (range 1.3+, 11.1). The Applicant submitted the results of the randomized, open-label CodeBreaK 200 trial of sotorasib versus docetaxel to verify the clinical benefit of sotorasib and support its conversion from accelerated to traditional approval for the same indication.

CodeBreaK 200 met its primary endpoint demonstrating a statistically significant improvement in PFS with a HR of 0.66 (95% CI: 0.51, 0.86). The observed treatment effect was marginal with only an approximately 5-week improvement in median PFS, which is shorter than the 6-week imaging interval. There was no difference in OS, with a

HR of 1.01 (95% CI: 0.77, 1.33) at the time of the primary analysis. The clinical significance of the 5-week difference in median PFS, in the absence of OS benefit, is uncertain. Additionally, the trial results are confounded by multiple sources of systemic bias raising concerns about whether CodeBreaK 200 can be considered an adequate and well-controlled trial.

Multiple features of CodeBreaK 200 do not appear consistent with an adequate and well-controlled trial:

- Given the high rate of early dropout on the docetaxel arm and potential loss of randomization, there were not adequate measures in place to minimize bias in patient assignment to treatment group, to assure comparability of the groups.
- Adequate measures were either not put in place, or not adequately followed to minimize bias on the part of investigators, given the rates of discrepancy between investigator and BICR calls for progression. Investigators, and likely patients as well, were eager to access sotorasib given its early success and differing route of administration and toxicity profile.
- Violations of the imaging charter, with confirmation of progression (COP) indirectly used to audit certain BICR assessments resulting in multiple sets of BICR reads, suggest there were not well defined and reliable methods to assess response.
- Issues in study conduct, high rates of censoring, loss of follow up of patients who withdrew consent, and potential loss of randomization may not allow for adequate analysis of the results of CodeBreaK 200 to assess the effect, and importantly magnitude of effect, of sotorasib vs docetaxel.

Both appropriate trial design and conduct are essential for an adequate and well-controlled trial, and to mitigate bias. It is important to have a plan to reasonably evaluate the treatment effect of a drug (i.e., trial design) and to carry out the plain faithfully (i.e., trial conduct). Strategies to mitigate bias in oncology clinical trials include:

- Allowing for crossover to reduce dropout from the control arm
- Patient education to reduce withdrawal of consent
- Investigator education to reduce bias related to imaging assessments
- Real-time BICR to reduce censoring related to discordant investigator and BICR assessments of disease progression
- Consent for OS follow-up even if patients dropout of the trial, to maximize collection of data for a more reliable assessment of OS

Crossover in CodeBreaK 200 was implemented with Protocol Amendment 3, but only after almost all patients (99%) had been enrolled at their respective trial sites.

Additionally, a number of patients had withdrawn from the trial without initiating study therapy by this time. The COP procedure was also instituted to minimize censoring related to discordant investigator and BICR assessments of disease progression; however, there was still discordance between investigator and BICR assessments. Furthermore, the imaging charter and protocol were violated, with the COP assessments indirectly used to audit the BICR assessments. Other potential strategies described above were either not adequate or put in place to mitigate bias.

FDA requests discussion of whether the results of CodeBreaK 200 can be reliably interpreted and whether CodeBreaK 200 can be considered an adequate and well-controlled trial.

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