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The latest developments from US FDA drug, biologic, and medical device advisory committee meetings.

October 5, 2023
Meeting Begin Time: 9:30 a.m. | **End Time:** 3:03 p.m.

IN THIS ISSUE

Oncologic Drugs Advisory Committee Meeting

AdComm Profiles and Voting Histories—Drugs/Biologics (IDRAC 175864)

Subject: Supplemental new drug application (sNDA) 214665/005: Lumakras (sotorasib) tablets, submitted by Amgen Inc, for the treatment of adult patients with Kirsten rat sarcoma viral oncogene homolog (*KRAS*) G12C–mutated locally advanced or metastatic non–small cell lung cancer, as determined by an FDA-approved test, who have received ≥1 prior systemic therapy.

Announced in the Federal Register
August 22, 2023 (IDRAC 370079)
(Volume 88, Number 161)

Today's Headline: PFS Endpoint Unreliable in Confirmatory Study for Amgen's Lumakras for NSCLC

Decision/Voting

A vast majority of the Oncologic Drugs Advisory Committee (ODAC) agreed that the primary endpoint—progression-free survival (PFS) per blinded independent central review (BICR)—in CodeBreaK 200, the confirmatory study conducted by Amgen Inc to support full approval of Lumakras (IDRAC 363620) (sotorasib), could not be reliably interpreted. Lumakras is approved under the accelerated approval (IDRAC 37909) pathway for the treatment of adult patients with Kirsten rat sarcoma viral oncogene homolog (*KRAS*) G12C–mutated locally advanced or metastatic non–small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received ≥1 prior systemic therapy. Many panelists stated that the lack of difference in overall survival (OS) between Lumakras and the active comparator supported the FDA's concerns about how the study was conducted, specifically the potential for bias in the radiological readouts and the execution of the study crossover (see *Clinical Issues*).

FDA Question(s) to the Committee	Vote		Comments
	Yes	No	
Can the primary endpoint, PFS per BICR, be reliably interpreted in CodeBreaK 200?	2	**10**	
NOTE: The FDA is not obligated to follow the voting recommendation of the advisory committee, but it may do so once all information is considered.			

Ahead of today's meeting, the sponsor submitted supplemental new drug application (IDRAC 37905) (sNDA) 214665/005 for Lumakras for the above indication to the FDA for consideration of full approval. Lumakras has been on the US market since May 2021 when it was granted accelerated approval. The sponsor was required to conduct a confirmatory study (CodeBreaK 200) to verify and describe the clinical benefit of Lumakras, which demonstrated a statistically significant improvement in PFS compared to docetaxel but no difference in OS. The panel was not asked to comment on the totality of the evidence supporting the sNDA or whether the FDA should grant Lumakras full approval. However, the patient and consumer representatives, along with a few other panelists, both considered the voting question to be "narrow."

In the Event Materials (IDRAC 371999), the FDA noted several issues with the conduct of CodeBreaK 200 and the potential for bias, especially given the uncertainty about the clinical significance of the 5-week difference in median PFS. The sponsor stated that it chose PFS as a primary endpoint to allow for the opportunity for crossover. However, the FDA had advised the sponsor a priori to use OS as the primary endpoint.

The committee members who agreed that PFS per BICR could be reliably interpreted said that the study met its primary endpoint based on the intent-to-treat analysis, demonstrating statistical significance. One panelist noted that the post hoc analyses were "informative, but they ultimately don't change the benefits that were, in fact, observed," and no Type 1 error was present. The other panel member who voted "yes" said that despite CodeBreaK 200 being a small trial, which is typical in the cancer setting, she recognized a "remarkably consistent effect." In the context of an open-label trial, statistically significant improvement in PFS in CodeBreaK 200 was "modest" but present, she added.

Both ODAC members who were in favor of the reliability of the PFS endpoint agreed that the quality of the BICR and the substantial variation that occurred between the first and second radiological interpretations were concerning. Some of the panelists who thought the endpoint could not be reliably interpreted stressed the importance of allowing Lumakras to remain on the market as a treatment option given its potentially more favorable formulation (tablet) and toxicity profile compared to other available therapies. The FDA informed the ODAC that it is not the agency's intention to remove Lumakras from the market, and multiple regulatory pathways are available to keep it approved while it is studied further.

The committee members who voted "no" explained that their decisions were influenced by the small sample size, "immediate" participant dropout in the docetaxel arm, crossover into the Lumakras arm without confirmed disease progression, investigator conduct, and the "small" 5-week PFS benefit. If the benefit had been greater and OS had been demonstrated, the panel may have come to "a different conclusion," one ODAC member said. However, many panelists commended the sponsor for choosing an active comparator (docetaxel). Ultimately, the integrity of the study data was impacted by the process used to perform the radiologic re-read, which triggered a subsequent reanalysis and introduced discrepancies between the 2 results.

One panelist said that Lumakras is a "highly anticipated agent in a hyper information age" where patients and providers have "high expectations." In light of the FDA's concerns about CodeBreaK 200 and the committee's discussion, this meeting is "call for our entire community" to develop strategies to mitigate the perception of equipoise to "balance hope with hype for new therapies for our patients," another ODAC member said. The agency agreed and said in its closing statement that today's discussion was a "call to action" to consider trial conduct and mitigation strategies in open-label trials in general.

Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence, highlighted the importance of clinical trial integrity. He said individuals should not participate in a clinical trial if they are not willing to accept an arm they do not prefer because it affects the "entire integrity of the clinical trial system." He also said this "whole discussion" could have "been avoided" if the "right" endpoint of OS were used in CodeBreaK 200 and noted that docetaxel was originally approved based on OS. Pazdur noted that certain steps could have been taken to mitigate some of the issues in CodeBreaK 200, such as real-time assessment of disease progression at the time of crossover, and it is "bothersome to see unidirectional dropout in clinical trials to this degree." In addition, "No amount of statistical machinations will address a poorly conducted trial."

Regarding oncology clinical trials in general, Pazdur expressed concern that the types of issues observed in CodeBreaK 200 are occurring more frequently in oncology clinical programs, although the problem is typically mitigated by OS results. Investigators should be committed to enrolling participants in a trial to follow through with the design rather than using the trial as a vehicle for patients to access certain treatments. The FDA will be following up with various professional groups and external symposiums to further discuss these issues, and the concern about investigator bias will be applied in the evaluation of oncology agents moving forward. "This will be a continuing discussion," he said.

Background Information

During this meeting, the Oncologic Drugs Advisory Committee (ODAC) met to consider supplemental new drug application (IDRAC 37905) (sNDA) 214665/005 for Lumakras (IDRAC 363620) (sotorasib [ATC: L01XX]) tablets, submitted by Amgen Inc, for the treatment of adult patients with Kirsten rat sarcoma viral oncogene homolog (*KRAS*) G12C–mutated locally advanced or metastatic non–small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received ≥1 prior systemic therapy. Lumakras is an inhibitor of *KRAS* G12C, a tumor-restricted, mutant-oncogenic form of KRAS.

As part of the sponsor's post-marketing requirement to verify and describe the clinical benefit of Lumakras, the sponsor conducted CodeBreaK 200, an open-label confirmatory clinical trial that randomized subjects 1:1 to receive either single-agent sotorasib or single-agent intravenous (IV) docetaxel. This sNDA proposes to convert the NDA (IDRAC 34571) to full approval based on the results from CodeBreaK 200, which met its primary endpoint, demonstrating a statistically significant improvement in progression-free survival (PFS).

The FDA also approved the therascreen KRAS RGQ PCR Kit (IDRAC 209371), from QIAGEN Manchester Ltd, and the Guardant360 CDx (IDRAC 319044), from Guardant Health, Inc, as companion diagnostics to determine if Lumakras is an appropriate treatment for patients. As noted in the Event Materials (IDRAC 371999), Lumakras was granted accelerated approval (IDRAC 37909) in May 2021 for the above indication. It was backed by data from CodeBreaK 100, a single-arm trial in participants with locally advanced or metastatic NSCLC with *KRAS* G12C mutations. The approval was based on an objective response rate (ORR) of 36% (95% confidence interval [CI]: 28, 45) and a median duration of response (DOR) of 10 months (range 1.3+, 11.1).

The American Cancer Society (ACS) notes that lung cancer is divided into 2 main types: NSCLC and SCLC. NSCLC accounts for approximately (~) 80-85% of lung cancers and includes 3 subtypes—adenocarcinoma, squamous cell carcinoma, and large cell carcinoma—that are grouped together as NSCLC since their treatment and prognoses are generally similar. In many NSCLC cases, individuals are tested for specific gene changes in the cancer cells.

Changes in the *KRAS* gene, which cause an abnormal *KRAS* protein to be made and contributes to the growth and spread of the cancer cells, are responsible for ~20-25% of NSCLCs, according to the ACS. NSCLCs with the *KRAS* mutation, which are mostly found in people with a history of smoking, are often classified as adenocarcinomas and are resistant to other drugs (e.g., epidermal growth factor receptor [EGFR] inhibitors). Of those diagnosed with NSCLC, ~13% have the specific *KRAS* G12C mutation.

Currently, only 2 targeted therapies, including Lumakras, are approved to treat NSCLC with a *KRAS* G12C mutation (see *Market Issues*), and neither have received full approval. These drugs attach to the *KRAS* G12C protein, helping to stop the growth of cancer cells, and are typically used to treat advanced NSCLC or patients who have received ≥1 other drug treatment. Prior to the approval of these agents, the "preferred" standard of care (SOC) regimen for these patients was single-agent docetaxel, which has a historical ORR of ~12%, according to the FDA.

The sponsor was required to conduct 2 randomized, multicenter post-marketing studies as a condition of accelerated approval. One study (CodeBreaK 200) was to evaluate participants with locally advanced or metastatic NSCLC with a history of prior systemic therapy for advanced disease and whose tumors harbor a *KRAS* G12C mutation. Another study (part B of the phase 2 CodeBreaK 100 study) was to further characterize serious adverse events (SAEs), including gastrointestinal toxicity, and to compare the safety and efficacy of Lumakras 960 mg daily versus a lower daily dose in subjects with locally advanced or metastatic *KRAS* G12C–mutated NSCLC who have received ≥1 prior systemic therapy.

The second study was issued as an additional post-market study after the FDA determined that analyzing spontaneous post-marketing AEs under section 505(k)(1) of the Federal Food, Drug, and Cosmetic Act (IDRAC 17027) (FD&C Act) "would not be sufficient" for assessing a known risk of AEs, including gastrointestinal toxicity, in patients receiving Lumakras [Draft Guidance: Postmarketing Studies and Clinical Trials - Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (Revision 1), October-2019 (IDRAC 301179)].

Given that the results of CodeBreaK 200 showed no difference in overall survival (OS), the clinical significance of the 5-week difference in median PFS is uncertain, the agency noted. Several additional concerns were highlighted in the event materials about potential bias and study conduct issues, including the announcement of positive results in multiple press releases from the sponsor (see *Regulatory History*), which contributed to "public awareness and interest" in Lumakras and "may have made the trial more susceptible to open-label bias." The agency asked the ODAC at today's meeting whether the results of CodeBreaK 200 could be reliably interpreted, especially given the "high uncertainty" in the magnitude of PFS benefit of Lumakras over docetaxel due to the marginal treatment effect on PFS.

The FDA noted that the methods to assess response were neither well defined nor reliable given the violations of the imaging charter and the indirect use of confirmation of progression (COP) to audit specific blinded independent central review (BICR) assessments, which resulted in multiple sets of BICR reads. An adequate analysis of the results of CodeBreaK 200 to determine the effect (and magnitude of effect) of Lumakras compared to docetaxel may not be possible due to issues in study conduct, high rates of censoring, loss of follow-up of patients who withdrew consent, and potential loss of randomization, according to the FDA. Considering these issues, the committee was also tasked with determining whether CodeBreaK 200 could be considered an adequate and well-controlled trial.

Proposed Indication

- *Lumakras (sotorasib) for the treatment of adult patients with* KRAS *G12C–mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received ≥1 prior systemic therapy.*

Proposed Dose

- *Lumakras 960 mg orally once daily.*

Regulatory History

June 29, 2018	The FDA issued a study-may-proceed letter for the initiation of CodeBreaK 100.
August 27, 2018	The first patient enrolled in CodeBreaK 100.
May 1, 2019	The FDA designated Lumakras an orphan drug for the treatment of *KRAS* G12C–positive NSCLC [How to Market Orphan Drugs (IDRAC 37910)].
June 3, 2019	The sponsor issued a press release regarding the investigation of Lumakras to announce the first clinical results from a phase 1 study that showed anti-tumor activity. The FDA noted that this announcement was made 1 year prior to the enrollment of the first patient into CodeBreaK 200.
August 16, 2019	The FDA granted fast track designation to Lumakras for the treatment of patients with previously treated metastatic *KRAS* G12C–mutated NSCLC [Marketing Authorization Procedures: Procedure for Priority Review/Accelerated Approval (IDRAC 37909)].
November 5, 2019	The sponsor and the FDA first discussed the study design for CodeBreaK 200 in a Type B pre–investigational new drug application (IND)/pre–phase 3 meeting [Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products, September 2023 (IDRAC 371476)]. The agency advised the sponsor to modify the study to assess OS as a primary endpoint and said that to potentially support a marketing application based on an improvement in PFS, the magnitude of effect on PFS would need to be "clinically meaningful" or "be supported by a statistically significant difference in OS."
May 29, 2020	The sponsor announced that it presented new data about Lumakras at the American Society of Clinical Oncology conference.
June 4, 2020	The first patient was enrolled in CodeBreaK 200.
July 6, 2020	The last patient was enrolled in CodeBreaK 100.
September 20, 2020	The sponsor announced that clinical data from CodeBreaK 100 were published in the *New England Journal of Medicine* [Hong DS, Fakih

	MG, Strickler JH, et al. *N Engl J Med*. 2020;383:1207-1217].
October 5, 2020	The sponsor announced positive topline results from CodeBreaK 100 indicating "durable anticancer activity" with Lumakras, which was 3 months after initiating CodeBreaK 200.
December 7, 2020	The agency granted breakthrough therapy designation (IDRAC 37909) to Lumakras for the treatment of patients with *KRAS* G12C–mutated NSCLC.
December 16, 2020	The sponsor submitted the Lumakras NDA to the FDA for accelerated approval [Application Format, Content and Submission (IDRAC 34571)]. At the time of this submission, 41% of participants were enrolled in CodeBreaK 200.
January 28, 2021	The FDA noted that the sponsor announced "detailed topline results" for CodeBreaK 100, which showed that Lumakras demonstrated a confirmed ORR and disease control rate (DCR) of 37.1% and 80.6%, respectively, and a median DOR of 10 months, demonstrating "rapid, deep, and durable responses," according to Amgen. In addition, Lumakras was considered the first *KRAS* G12C inhibitor to show PFS (median of 6.8 months) in a phase 2 study.
February 9, 2021	The FDA and the sponsor participated in a Type B guidance meeting to discuss changes to the statistical analysis plan (SAP) for CodeBreaK 200 based on the agency's concerns about "equipoise" and ensuring access to Lumakras for participants who progressed on treatment with docetaxel. In addition, the sponsor proposed to 1) reduce the sample size from 650 to 330 subjects but maintain a 1:1 randomization, 2) conduct an interim analysis at an information fraction of ~70%, and 3) allow crossover from the docetaxel group.
February 15, 2021	Protocol Amendment 3 was implemented for CodeBreaK 200, which instituted the changes to the SAP discussed at the February 9 meeting and allowed for study crossover [21 CFR part 312.30 (IDRAC 8714)].
February 16, 2021	The sponsor announced that the FDA granted the Lumakras NDA priority review (IDRAC 37909) for the treatment of advanced or metastatic NSCLC.
March 10, 2021	The first implementation of the crossover occurred in CodeBreaK 200.
April 26, 2021	The last patient was enrolled in CodeBreaK 200.
May 28, 2021	Based on results from CodeBreaK 100, the FDA approved NDA 214665 for Lumakras (IDRAC 333122) under the accelerated approval pathway for the treatment of adult patients with *KRAS* G12C–mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received ≥1 prior systemic therapy [FDA Press Release (IDRAC 330585)].
	The FDA approved the therascreen KRAS RGQ PCR Kit and the Guardant360 CDx as companion diagnostics to determine if Lumakras is an appropriate treatment for patients.
April 5, 2022	The sponsor provided an updated interim PFS analysis to the FDA at 74% information fraction, which showed that the PFS per BICR results "were not initially statistically significant." However, after a discrepancy was noted between investigator and BICR assessments, the BICR radiologists re-read discordant scans, leading to updated PFS results that were considered statistically significant.
May 5, 2022	At an ad hoc meeting, the FDA and the sponsor discussed the updated PFS interim analysis results and BICR re-reads. The agency noted concerns about the lack of adherence to the protocol and imaging charter. The sponsor requested submission of a marketing application based on this analysis, but the FDA advised against it and recommended a global re-read of all scans.
October 21, 2022	The sponsor and the FDA participated in a Type B pre-sNDA meeting (IDRAC 371476) to discuss the results of CodeBreaK 200 and plan for an sNDA submission.
September 12, 2022	The sponsor announced the topline results for CodeBreaK 200.

November 21, 2022	The FDA approved sNDA 214665/002 (IDRAC 355933) to update the Effects of Lumakras on Other Drugs and Pharmacokinetics sections of the US Prescribing Information based on the results from Study 20200426, which evaluated the effect of coadministration of Lumakras on the pharmacokinetics of rosuvastatin.
January 20, 2023	The FDA approved sNDA 214665/003 (IDRAC 358952) to add a 320 mg dosage strength of Lumakras and add an alternate site for release and stability testing.
February 24, 2023	The sponsor submitted an sNDA for the conversion from accelerated approval to traditional approval for Lumakras based on CodeBreaK 200.
March 17, 2023	The FDA approved sNDA 214665/007 (IDRAC 362630) to make corrections to the Lumakras carton and container labeling for the 320 mg and 90 mg tablets.
April 24, 2023	The FDA approved sNDA 214665/004 (IDRAC 363620) to update the Hepatic Impairment and Pharmacokinetics sections of the US Prescribing Information based on the results from Study 20200362, which evaluated the pharmacokinetics of Lumakras to fulfill a post-marketing requirement.

Regulatory Issues

Section 505(d) of the FD&C Act requires demonstration of "substantial evidence" of effectiveness through adequate and well-controlled studies for a drug or biologic to receive FDA approval. To establish effectiveness, the effect of the drug must be distinguished from influences (e.g., biased observation). Section 115(a) of the Food and Drug Administration Modernization Act (IDRAC 81767) (FDAMA) gives the FDA the authority to determine, "based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness," as explained in the agency's Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, December-2019 (IDRAC 304030).

Per 21 CFR 314.126 (IDRAC 8993), important characteristics of an adequate and well-controlled trial include 2 elements pertaining to bias:

- The method used to assign patients to treatment and control groups should minimize bias as it is intended to assure comparability of the groups in terms of important variables (e.g., age, sex, severity of disease, duration of disease, use of drugs or therapy other than the test drug).
- Adequate measures should be taken to minimize bias on the part of the subjects, observers, and data analysts.

In the Event Materials (IDRAC 371999), the FDA noted "multiple indications of systemic bias observed related to study conduct" in CodeBreaK 200, including the following:

- The high rate of early dropout in the docetaxel arm and potential loss of randomization suggest that adequate measures were not in place to minimize bias in the patient assignment to the treatment group.
- Given the rates of discrepancy between investigator and BICR calls for progression, adequate measures were either not in place or were not adequately followed to minimize bias on the part of investigators.

Accelerated Approval

To help expedite the development of drugs intended to treat serious or life-threatening diseases and conditions, the FDA uses several approaches, such as the accelerated approval program. The agency initiated this program to allow for earlier approval of products that fill an unmet medical need based on a surrogate endpoint. Accelerated approval is explained further in the FDA's Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (Final), May-2014 (Updated: 25-June-2020) (IDRAC 343947). The guidance also outlines additional routes for expedited review, such as fast track, priority review, and breakthrough therapy designations, which the original NDA for Lumakras received.

Per section 506(c) of the FD&C Act, as amended by section 901 of the Food and Drug Administration Safety and Innovation Act (IDRAC 146311) (FDASIA), and 21 CFR 314.500, subpart H (IDRAC 8838) (for drugs) or 21 CFR 601.41, subpart E (IDRAC 26695) (for biological products), the FDA may grant accelerated approval to a product for a serious or life-threatening disease or condition after it has determined "that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."

To obtain traditional approval, sponsors must conduct confirmatory trials to verify benefit for products that are granted accelerated approval. These post-marketing clinical studies are intended to demonstrate substantial evidence of effectiveness on a clinically meaningful endpoint or validated surrogate.

Regulatory Programs to Support Oncology Product Review

The FDA conducted the Lumakras NDA review as part of Project Orbis, an FDA Oncology Center for Excellence (OCE) initiative, in collaboration with the Australian Therapeutic Goods Administration (TGA), the Brazilian Health Regulatory Agency (ANVISA), Health Canada, and the United Kingdom's (UK's) Medicines and Healthcare products Regulatory Agency (MHRA). Project Orbis is an initiative developed by the OCE in 2019 and described at a 2021 Grand Rounds meeting [FDA Workshop Bulletin, 13-May-2021 (IDRAC 332593)]. The project provides "a framework for concurrent submission and review of oncology products among international partners," according to the agency.

The review of the Lumakras NDA was conducted under the Real-Time Oncology Review (RTOR) pilot program, the Assessment Aid, and the Product Quality Assessment Aid (PQAA), which were voluntary submissions from the sponsor to facilitate the FDA's assessment. The FDA's Draft Guidance for Industry: Real-Time Oncology Review (RTOR) Guidance for Industry, July-2022 (IDRAC 350656) provides recommendations to sponsors on the process for submitting selected NDAs and biologics license applications (IDRAC 34571) with oncology indications for review under the RTOR. The pilot program streamlined the submission of the Lumakras data prior to the sponsor's filing of the entire application. The Assessment Aid is intended to focus the agency's review on "critical thinking (assessment)," increase review efficiency and consistency, and decrease review time spent on administrative tasks (e.g., formatting).

Clinical Issues

To support full approval of the Lumakras NDA, the sponsor submitted data from CodeBreaK 200, an ongoing study to evaluate the efficacy and safety of Lumakras versus docetaxel in participants with previously treated, locally advanced and unresectable or metastatic NSCLC with a *KRAS* G12C mutation. Radiographic tumor assessments were conducted at the time of screening, every 6 weeks through week 49, then at 9-week intervals. Participants were to receive treatment until independent central COP, intolerance of treatment leading to discontinuation, initiation of another anticancer therapy, or withdrawal of consent. In the Event Materials (IDRAC 371999), the FDA acknowledged "the obligatory nature" of the open-label study design given the routes of administration and differing toxicity profiles. Table 1 provides additional information about CodeBreaK 200.

Table 1. Lumakras Clinical Program

Trial	Design	Regimen	No. Patients	Primary Endpoint
CodeBreaK 200	Multicenter, randomized, open-label, active-controlled phase 3 study	1:1 randomization*: • Oral Lumakras 960 mg once daily *or* • IV docetaxel 75 mg/m^2 every 3 weeks	345	PFS per RECIST v1.1 as assessed by BICR

RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1
*Participants were stratified at randomization based on the number of prior lines of therapy for advanced disease (1 versus 2 versus >2), race (Asian versus non-Asian), and history of central nervous system involvement (present versus absent).

Based on the response rate of Lumakras in CodeBreaK 100, the sponsor and the FDA discussed protocol amendments to CodeBreaK 200 to "mitigate potential issues of open-label bias." Changes to the SAP for CodeBreaK 200 resulted in 1) a reduction in sample size from 650 to 330 participants while maintaining the 1:1 randomization and 2) an allowance for crossover.

Crossover from the docetaxel group to the Lumakras group was not permitted at the time of study initiation but was instituted with Protocol Amendment 3. In the study, 99% of participants enrolled before Protocol Amendment 3 was implemented at their respective study sites. After the investigator determined that a participant had radiologic progression, they were permitted to 1) continue to receive the investigational product (for subjects in both groups) or 2) cross over and receive Lumakras (for subjects in the docetaxel group only).

Once crossover was built into the protocol with Protocol Amendment 3, a COP procedure was implemented. The FDA noted that despite the sponsor's claim that the crossover procedure also required independent central review before continuing therapy beyond disease progression or crossing over to Lumakras for participants on the docetaxel arm, this independent central review process was by a COP procedure, rather than BICR. "The COP procedure was completely different and separate from the BICR assessment of radiographic disease progression," the agency stated. An independent COP radiologist—separate from the BICR radiologist—was required to review scans within 3 business days after an investigator's assessment of disease progression.

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 evaluations in a BICR-assessed PFS endpoint when crossover is a feature of a trial. The purpose of the COP reading was to provide site investigators with a second independent assessment about whether the participant had progressive disease.

Safety

The safety analysis was based on the safety analysis set and included all participants in the full analysis set (FAS) who received ≥1 dose of the investigational product (Lumakras: n = 169; docetaxel: n = 151). In the Lumakras arm, all-cause treatment-emergent AEs (TEAEs) of grade ≥3 occurred in 94 (56%) of participants, compared to 84 (56%) of participants in the docetaxel arm. Fatal TEAEs occurred equally in 11 (7%) of participants in both groups. At the time of the primary analysis in the efficacy population, 64% of participants had died in the Lumakras arm compared to 54% in the docetaxel arm. However, the death rates were similar for both efficacy and safety populations and when evaluating subjects who received ≥1 dose of the study therapy. No new safety signals were identified for Lumakras in CodeBreaK 200.

Efficacy

The efficacy analyses of the primary and key secondary endpoints for CodeBreaK 200 comparing Lumakras to docetaxel were conducted on the FAS, which was considered the intent-to-treat (ITT) population. The required sample size was 330 participants with ~230 PFS events required for the final analysis. An interim analysis was planned for PFS when an information fraction of ~70% of the targeted PFS events was observed from both groups or when enrollment was complete and the final randomized subject had a 6-week follow-up—whichever occurred later. The testing procedure specified that if PFS were significant, ORR and OS would each be tested, with a proportion of the allocated Type I error of PFS being "recycled to each endpoint." In addition, patient-reported outcome (PRO) endpoints would only be tested if PFS, ORR, and OS were significant.

The FDA noted that the interim analysis of PFS did not meet the O'Brien-Fleming spending boundary calculated based on 171 events reported at the time of the analysis. Another ad hoc interim analysis was conducted based on updated data for 12 participants in the docetaxel group and 1 in the Lumakras group. The independent data monitoring committee reviewed the results and recommended that the trial continue without stopping and that a global re-reading of scans be performed for the final PFS analysis. At the time of the final analysis, which occurred when 223 PFS events were reached, 46 participants who were treated with docetaxel and had progressive disease per the investigator had crossed over to receive Lumakras.

The primary endpoint of CodeBreaK 200 was PFS by BICR. Secondary endpoints included OS, ORR, and PROs. The FDA noted that while the estimated PFS HR across analyses is "generally consistent," 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." Further elaboration on the robustness of the PFS primary endpoint is provided in the Event Materials (IDRAC 371999). Table 2 shows the efficacy results for the primary and secondary endpoints in CodeBreaK 200.

Table 2. Efficacy Results for CodeBreaK 200

	Lumakras (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 Lumakras, 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)

The FDA noted that the nature of PFS as an endpoint is "subjective," which could lead to variation in outcome assessments across different assessors. To counter this subjectivity, it is essential that—when measuring efficacy—the magnitude of treatment effect on PFS is large enough to overcome potential variability. The following concerns about magnitude of PFS benefit of Lumakras over docetaxel are explained in greater detail in the Event Materials (IDRAC 371999):

- The observed improvement in median PFS (i.e., 5 weeks) is less than the 6-week imaging interval. The "true" median PFS benefit may be <5 weeks and as small as 5 days.
- Asymmetric early dropouts occurred with 23 (13%) of 174 patients randomized to docetaxel compared to 2 (1%) of 171 patients randomized to Lumakras who did not receive any study therapy. It is unknown to what extent the PFS treatment effect would have changed and in what direction it would have changed if the patients had stayed in the study.
- Investigator-based assessments of PFS favored Lumakras.
- Patients in the docetaxel arm crossed over early to Lumakras treatment before BICR-assessed progressive disease.
- The imaging charter and protocol were not consistently adhered to, resulting in multiple BICR assessments of the PFS primary endpoint.

In the primary analysis, OS did not demonstrate a survival advantage with Lumakras over docetaxel, and the OS Kaplan-Meier plot indicated no separation between curves for participants in either group, suggesting a lack of benefit and an inability to "definitely rule out potential detriment." In addition, the FDA noted that 19 of 46 participants who were assessed by investigators to have progressive disease did not have BICR confirmation of progressive disease before crossing over to receive Lumakras. The PRO-based endpoints are considered exploratory, and the FDA stated that interpretation of PRO-based endpoints is difficult "from a clinical perspective" since the potential for bias exists in the estimation of treatment effects. This resulted in the lack of a formal assessment of clinical meaningfulness from the patient perspective.

Medical Issues

Lung cancer is the third most common cancer and the type of cancer that results in more deaths than any other cancer in the US, according to the Centers for Disease Control and Prevention (CDC). In 2020, 197,453 new lung cancers were reported in the US, and 136,084 deaths were attributable to lung cancer. Between 2016 and 2020, almost half of all lung cancer cases were diagnosed at a later stage when the cancer had spread from the lungs to more distant parts of the body. Smoking is a major cause of lung cancer, and ~9 out of 10 lung cancer deaths in the US are caused by smoking cigarettes or exposure to secondhand smoke,

the CDC notes. In addition, >7,300 nonsmokers die each year from lung cancer due to secondhand smoke.

Approaches to cancer treatment depend on the type of cancer, the disease stage, and an individual's age and their overall health. While the goal of treatment is to cure cancer, many people without the option of a cure attempt to control the disease or reduce symptoms for as long as possible. As noted in the Event Materials (IDRAC 371999), ~40-50% of patients with advanced NSCLC will respond to chemotherapy/immunotherapy combinations as first-line treatment. However, most patients will progress while taking standard first-line therapies or after they have completed treatment.

Patients with NSCLC are treated with surgery, radiofrequency ablation, radiation therapy, chemotherapy, targeted drug therapy, immunotherapy, palliative procedures, or a combination of those treatments, according to the ACS. Those who have the *KRAS* G12C mutation will typically be treated with a targeted therapy drug (i.e., Lumakras, adagrasib [Krazati (IDRAC 367599), from Mirati Therapeutics, Inc]) after trying other drugs.

Pharmacology Issues

As noted previously, Lumakras inhibits *KRAS* G12C. KRAS is a RAS guanosine triphosphatase (GTPase), and *KRAS* G12C is a tumor-restricted, mutant-oncogenic form of KRAS. Lumakras forms an irreversible, covalent bond with the unique cysteine of *KRAS* G12C, which locks the protein in an inactive state and prevents downstream signaling without affecting wild-type *KRAS*. Lumakras blocked *KRAS* signaling, prevented cell growth, and encouraged apoptosis only in *KRAS* G12C tumor cell lines and inhibited *KRAS* G12C *in vitro* and *in vivo* with minimal detectable off-target activity. Treatment with Lumakras led to tumor regressions and prolonged survival in mouse tumor xenograft models and was associated with anti-tumor immunity in *KRAS* G12C models. The product label notes that Lumakras exposure-response relationships and the time course of the pharmacodynamic response are unknown.

In the Event Materials (IDRAC 371999), the FDA noted that KRAS has been considered an "undruggable" target for most of the past 4 decades since it was discovered. Various factors contributed to a lack of progress in targeting the protein, including affinity of KRAS for GTP and high intracellular concentrations of GTP—which contribute to higher concentrations of the active GTP-bound KRAS—and the lack of binding sites on the smooth protein surface. After the switch pocket II of the KRAS protein was discovered, a breakthrough led to the development of molecules that specifically target the cysteine residue in *KRAS* G12C–mutant proteins. This results in the trapping of the protein in the inactive, guanosine diphosphate (GDP)–bound state and the prevention of downstream proliferation and signaling.

Market Issues

When Lumakras was first approved under accelerated approval in the US in 2021, it was the first and only targeted therapy available to treat patients with *KRAS*-mutated NSCLC [FDA Press Release-28-May-2021 (IDRAC 330585)]. Prior to the approval of Lumakras, tumors with *KRAS* mutations were generally considered resistant to drug therapy, according to the FDA. In December 2022, the agency approved a second targeted therapy, Krazati (IDRAC 367599) (adagrasib), from Mirati Therapeutics, Inc, under accelerated approval for the same indication as Lumakras. If the FDA converts the approval of Lumakras from accelerated to traditional approval, it will be the first targeted therapy approved in the US outside of the accelerated approval pathway for the treatment of patients with NSCLC with a *KRAS* G12C mutation.

The agency noted in the Event Materials (IDRAC 371999) that because Lumakras and Krazati are approved under accelerated approval, they are not considered "available therapy" per the FDA's Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (Final), May-2014 (Updated: 25-June-2020) (IDRAC 343947).

Some chemotherapy agents are approved to treat patients with metastatic NSCLC after prior platinum chemotherapy and anti–programmed death-ligand 1 (PD-L1)–based therapy. Docetaxel and pemetrexed are single-agent chemotherapy treatments approved to treat locally advanced or metastatic NSCLC after platinum therapy failure or after prior chemotherapy, respectively. Docetaxel and ramucirumab [Cyramza (IDRAC 344615), from Eli Lilly and Company] are approved as a combination chemotherapy to treat metastatic NSCLC with disease progression on or after platinum-based therapy.

Lumakras is approved for use in multiple countries to treat NSCLC. The European Commission (EC) in the European Union (EU) and the MHRA in the UK conditionally approved sotorasib under the trade name Lumykras in January 2022 and September 2021, respectively, for the treatment of adults with advanced NSCLC with *KRAS* G12C mutation and who have progressed after ≥1 prior line of systemic therapy [EMA EPAR EMEA/H/C/005522 Revision 1: LUMYKRAS (sotorasib), 29-November-2022 (IDRAC 356221); Marketing Authorization Procedures: Review, Communication and Approval (UK) (IDRAC 506)]. Health Canada also approved Lumakras in September 2021 for the treatment of adult patients with *KRAS* G12C–mutated locally advanced (not amenable to curative therapy) or metastatic NSCLC who have received ≥1 prior systemic therapy [Summary Basis of Decision (SBD) and Product Monograph (PM): LUMAKRAS (sotorasib), 07-December-2021 (IDRAC 340954)]. Health Canada and the MHRA approved the product after review under Project Orbis.

In January 2022, Japan's Ministry of Health, Labour and Welfare (MHLW) approved Lumakras for the treatment of positive *KRAS* G12C–mutated, unresectable, advanced, and/or recurrent NSCLC that has progressed after systemic anticancer therapy [Marketing Authorization Procedures: Review, Communication and Approval (JP) (IDRAC 16686)]. In 2021, the Ministry of Health and Prevention in the United Arab Emirates approved Lumakras for an NSCLC indication, and in November 2021, the Hainan BoAo government in China granted early access to Lumakras in designated hospitals in the province. Lumakras is currently under regulatory review in Latin American, Middle Eastern, African, and Asian Pacific countries.

In the Pipeline

Opnurasib. Opnurasib (JDQ443), an inhibitor of the *KRAS* G12C mutation, is under evaluation in a randomized, controlled, open-label phase 3 study (KontRASt-02) to determine the efficacy and safety of the product in comparison with docetaxel in ~360 previously treated subjects with locally advanced or metastatic *KRAS* G12C–mutant NSCLC. Novartis is recruiting ~360 participants who are randomized to receive either opnurasib or docetaxel and have the opportunity to cross over to opnurasib at disease progression per RECIST 1.1 confirmed by BIRC. The primary outcome measure is PFS up to 24 months, and several secondary endpoints also evaluate survival, including OS, overall response rate, and DOR. Begun in June 2022, the study is estimated to complete in December 2025.

Divarasib. Genentech, Inc, is recruiting ~498 participants with advanced or metastatic solid tumors with a *KRAS* G12C mutation for an open-label, dose-escalation and dose-expansion phase 1a/1b study to evaluate the safety, pharmacokinetics, and activity of divarasib (GDC-6036), a covalent *KRAS* G12C inhibitor, as a single agent and in combination with other anti-cancer therapies. Participants are divided into 1 of 7 treatment arms; only 1 arm is evaluating divarasib as a single agent. In stage 1 of the single-agent arm, participants receive divarasib orally once daily with an increased dose in successive cohorts until a study-specific threshold is reached. The primary outcome measures are the percentage of participants with AEs and dose-limiting toxicities. The study began in July 2020 and is estimated to complete in November 2024.

Of the participants enrolled as of August 24, 2023, 60 with NSCLC received divarasib [Sacher A, LoRusso P, Patel MR, et al. Single-agent divarasib (GDC-6036) in solid tumors with a *KRAS* G12C mutation. *N Engl J Med*. 2023;389(8):710-721]. AEs were mostly low grade, and a confirmed response was observed in 53.4% of participants (95% CI: 39.9, 66.7). The median PFS was 13.1 months (95% CI: 8.8, could not be estimated). The investigators determined that treatment with divarasib resulted in "durable clinical responses" across tumors positive for *KRAS* G12C.

LY3537982. Eli Lilly and Company, in collaboration with Loxo Oncology, Inc, and Merck Sharp & Dohme Corp (Merck), is recruiting ~400 participants for a multicenter, open-label phase 1a/1b study to evaluate the safety, tolerability, and preliminary efficacy of oral LY3537982 in participants with *KRAS* G12C–mutant solid tumors. The study is evaluating LY3537982, a selective covalent *KRAS* G12C inhibitor, as a single agent and in combination with other agents. The primary outcome measures are the recommended phase 2 dose of LY3537982 monotherapy, the safety and tolerability of LY3537982 when administered alone or in combination with other investigational agents, and the optimal dose of LY3537982 to be administered to treatment-naïve participants with advanced NSCLC in combination with pembrolizumab [Keytruda (IDRAC 369786), from Merck]. Efficacy (anti-tumor activity) was

evaluated as a secondary outcome measure. The study, which began in July 2021, is estimated to be completed in September 2025.

In April 2023, initial results from the study were presented at the American Association for Cancer Research Annual Meeting. Of the participants enrolled as of the date of the meeting, 16 had NSCLC and received LY3537982. Among those who were evaluable for efficacy, 9 with *KRAS* G12C–mutated NSCLC had previously received treatment, and 5 had the mutation but were naïve to treatment. The overall response rate and partial response in participants naïve to treatment were both 60%; they were both 0% in those who previously received treatment. TEAEs reported in ≥10% of participants were mostly grade 1, and no serious treatment-related SAEs or deaths were reported.

Additional *Cortellis RI* Resources Briefing Information

Event Materials (IDRAC 371999)

AdComm Bulletin and *FDA Workshop Bulletin* Coverage

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