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CADTH Reimbursement Recommendation

Sotorasib (Lumakras)

Indication: For the treatment of adult patients with Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C-mutated locally advanced (not amenable to curative therapy) or metastatic non–small cell lung cancer (NSCLC) who have received at least one prior systemic therapy.

Sponsor: Amgen Canada Inc.

Final recommendation: Do not reimburse

Summary

What Is the CADTH Reimbursement Recommendation for Lumakras?

CADTH recommends that public drug plans should not reimburse Lumakras for the treatment of adult patients with Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C-mutated locally advanced (not amenable to curative therapy) or metastatic non–small cell lung cancer (NSCLC) who have received at least 1 prior systemic therapy.

Why Did CADTH Make This Recommendation?

- The clinical evidence reviewed by CADTH was insufficient to conclude that treatment with Lumakras results in a clinically meaningful delay in disease progression compared with docetaxel. It was impossible to assess whether treatment with Lumakras would prolong survival relative to docetaxel.
- Patients identified the need for more effective treatments that delay disease progression, prolong survival, control disease symptoms, improve quality of life, reduce side effects, and offer an oral route of administration. While Lumakras offers an oral route of administration, it is not clear whether Lumakras meets the other needs identified by patients.

Additional Information

What Is KRAS G12C-Mutated NSCLC?

NSCLC occurs when healthy cells in the lung become cancerous and is considered metastatic when cancer cells have spread to other parts of the body. Approximately 30,000 new cases of NSCLC are diagnosed each year in Canada. Approximately 7.9 per 100,000 patients with NSCLC have KRAS G12C mutations, which can lead to poor disease outcomes.

Unmet Needs in KRAS G12C-Mutated NSCLC

There are limited treatment options for patients with KRAS G12C-mutated NSCLC who have progressed on standard therapy. Effective treatments that can be administered orally, prolong survival, improve quality of life, and have fewer side effects are needed.

How Much Does Lumakras Cost?

Treatment with Lumakras is expected to cost approximately $10,806 per 28 days.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that sotorasib not be reimbursed for the treatment of adult patients with Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C-mutated locally advanced (not amenable to curative therapy) or metastatic non–small cell lung cancer (NSCLC) who have received at least 1 prior systemic therapy.

Rationale for the Recommendation

pERC review 1 phase III, multicentre, randomized controlled trial (CodeBreaK 200) of sotorasib versus docetaxel in adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC who have received at least 1 prior systemic therapy was reviewed by pERC. Although the CodeBreaK 200 study resulted in a between-group difference of approximately 1 month in median progression-free survival (PFS) in favour of sotorasib compared to docetaxel (stratified hazard ratio [HR] = 0.66; 95% confidence interval [CI], 0.51 to 0.86), pERC remained uncertain whether the absolute benefit in median PFS was clinically meaningful. Further, it was not possible to assess whether treatment with sotorasib would result in an overall survival (OS) benefit as CodeBreaK 200 was not powered for this outcome (at a median follow-up time of approximately 18 and 16 months in the sotorasib and docetaxel groups, respectively, the OS HR was 1.01; 95% CI, 0.77 to 1.33). pERC also considered that sotorasib appeared to be associated with considerable toxicity. Comparative safety from the CodeBreaK 200 trial indicated that grade 3 and 4 adverse events (AEs) were more common in patients treated with sotorasib. Overall, pERC agreed that there was insufficient evidence to conclude that sotorasib has a more favourable toxicity profile than docetaxel.

Patients identified a need for more effective treatments that delay disease progression, prolong survival, control disease symptoms, improve quality of life, reduce side effects, and offer an oral route of administration. Although pERC acknowledged that sotorasib meets the need for an oral drug option, pERC could not conclude that sotorasib would meaningfully delay disease progression compared to docetaxel. Furthermore, there was no OS benefit compared to docetaxel in the CodeBreaK 200 trial. pERC could not reach definitive conclusions regarding the effects of sotorasib compared to docetaxel on health-related quality of life (HRQoL) and disease symptoms due to a significant decline in the number of patients available to provide assessments over time and the open-label and descriptive nature of the analyses.

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse sotorasib for the treatment of adult patients with KRAS G12C-mutated locally advanced (not amenable to curative therapy) or metastatic NSCLC who have received at least 1 prior systemic therapy. pERC discussed each of the issues identified by the sponsor in their request for reconsideration. pERC also reviewed and discussed the feedback from patient groups, clinical experts, and clinician groups on the initial draft recommendation.

- During the initial and reconsideration meetings, pERC recognized the need for additional treatment options in patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, given the poor prognosis and high symptom burden in this patient population. pERC acknowledged and carefully deliberated on the statistically significant improvement in PFS, the absolute benefit in median PFS, the PFS HR, and PFS probabilities at various time points. pERC noted that PFS may be an important outcome for patients and clinicians, which was reflected in their feedback on the initial draft recommendation. However, most of the committee members remained uncertain whether the magnitude of the improvement compared to docetaxel was clinically meaningful. pERC concluded that there is insufficient evidence that sotorasib will meaningfully delay disease progression, provide clinically meaningful improvements in HRQoL, or address the unmet needs identified by stakeholders for patients living with KRAS G12C-mutated locally advanced or metastatic NSCLC.
- During the initial and reconsideration meetings, pERC noted that OS is an important outcome based on patient and clinician input. Although OS was a key secondary end point in the CodeBreaK 200 trial, the OS analysis was not adequately powered following a protocol amendment. Key limitations of the OS results included patients in the docetaxel group crossing over to the sotorasib group and a likely violation of the proportional hazards assumption. Overall, pERC was uncertain whether the modest PFS benefit with sotorasib would translate into a meaningful OS benefit compared to docetaxel.
- Although the CodeBreaK 200 study demonstrated that treatment with sotorasib resulted in benefits in objective response rate (ORR) (ORR = 28.1%; 95% CI, 21.5 to 35.4 versus 13.2%; 95% CI, 8.6 to 19.2), pERC discussed that the responses did not translate into clinically meaningful delays in disease progression.
- pERC noted the relatively higher proportion of randomized patients in the docetaxel compared to the sotorasib group who did not receive study treatment. This difference contributed to an imbalanced censoring between study groups and a higher proportion of patients whose response could not be assessed in the docetaxel group. Although pERC discussed that the extent and direction of any bias stemming from these imbalances cannot be determined, pERC remained concerned about the resulting uncertainty in treatment effects.
- During the reconsideration meeting, pERC deliberated on feedback provided by the sponsor, patient and clinician groups, which suggested that sotorasib has a manageable and favourable toxicity profile compared to docetaxel. In light of the feedback received pERC redeliberated the harms results of CodeBreaK 200. The committee remained concerned about the higher proportion of patients experiencing gastrointestinal (GI) toxicity (i.e., diarrhea, vomiting, and abdominal pain) and grade 3 and 4 AEs in the sotorasib group and the risk of bias in the reporting of AEs due to the open-label design of the CodeBreaK 200. pERC reiterated that the HRQoL data analyzed in CodeBreaK 200 were challenging to interpret, given the exploratory nature, open-label design, and significant decline in the number of patients available to provide assessments over time. Overall, pERC agreed that there was insufficient evidence to conclude that sotorasib has a more favourable toxicity profile than docetaxel.
- pERC noted that Health Canada had reviewed efficacy and safety data from CodeBreaK 100 as the pivotal study for the indication under review. CodeBreaK 100 was a multicentre, noncomparative,

open-label, single-arm phase II study. pERC's review focused on the subset of patients with KRAS G12C mutated advanced NSCLC who had received at least 1 prior systemic therapy (n = 126) and were enrolled into phase II of CodeBreaK 100. The ORR was 37.4% (95% CI, 28.84 to 46.58). pERC acknowledged high uncertainty regarding the magnitude of clinical benefit due to the noncomparative, open-label study design, and the small sample size.

Background

Lung cancer is 1 of the most diagnosed cancers, with NSCLC accounting for approximately 80% to 88% of all lung cancer diagnoses in Canada. In 2020, the incidence of NSCLC in Canada was estimated to be 60.5 per 100,000 persons. In 2021, an estimated 29,600 new cases of lung cancer and 21,150 deaths due to lung cancer were projected. Survival from lung cancer across all stages and histologies is poor, with a 5-year net survival rate of 22%. NSCLC often remains asymptomatic until the disease is in its advanced stages. When patients with NSCLC present with symptoms, these are usually nonspecific and difficult to attribute to lung cancer. Advanced NSCLC is associated with a higher prevalence and intensity of symptoms such as pain, dyspnea, cough, decreased appetite, weight loss and depression, as well as lower HRQoL compared to other advanced cancers. As early diagnosis of NSCLC is challenging, approximately two-thirds of patients with NSCLC have advanced or metastatic disease at diagnosis when curative treatments are not possible. Median OS of patients with metastatic NSCLC (stage IV, A and stage IV, B) is poor, ranging from 8 to 11 months; 5-year OS ranges from 4% to 6%. The 5-year net survival rate for stage IV NSCLC is 5.2%.

NSCLC often holds oncogenic driver mutations, leading to uncontrolled cell growth and proliferations. Of these, mutations within the rat sarcoma viral oncogene homologue (RAS) family account for over 30% of all mutated oncogenes in NSCLC, causing approximately 1 million deaths worldwide annually. Within the RAS family, KRAS is the isoform most frequently altered in NSCLC. Approximately 1 in 4 patients with NSCLC harbour KRAS mutations. Patients with KRAS-mutated NSCLC have a lower proportion of response to cytotoxic chemotherapy and decreased survival compared to the overall population of patients with NSCLC. The KRAS G12C subtype (KRAS G12C) represents almost half of all KRAS mutations in NSCLC and is identified in approximately 13% of patients with NSCLC. Based on an estimation in the Health Canada Reviewers Report, the incidence of patients living in Canada with NSCLC harbouring the KRAS G12C mutation was approximately 7.9 per 100,000 persons.

Health Canada has approved sotorasib for the treatment of adult patients with KRAS G12C-mutated locally advanced (not amenable to curative therapy) or metastatic NSCLC who have received at least 1 prior systemic therapy. Sotorasib is a highly selective inhibitor of KRAS G12C that suppresses the rapid proliferation of cancer cells. It is available as oral tablets, and the dosage recommended in the product monograph is 960 mg (8 × 120 mg tablets) orally once daily until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 randomized, open-label, multicentre phase III study in adult patients with KRAS G12C-mutated NSCLC who progressed after prior platinum-based chemotherapy and a checkpoint inhibitor; and a review of 1 nonrandomized, open-label, single-arm phase I/II study in adult patients with KRAS G12C-mutated advanced NSCLC
- patients' perspectives gathered in 1 joint input by 3 patient groups: Lung Health Foundation (LHF, formerly the Ontario Lung Association), Lung Cancer Canada (LCC), and the Canadian Cancer Survivor Network (CCSN)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with NSCLC
- input from 2 clinician groups, Ontario Health – Cancer Care Ontario (OH-CCO)'s Lung Cancer Drug Advisory Committee (LC DAC) and LCC
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

The LHF, LCC, and the CCSN submitted a joint patient group input. A total of 5 people (4 patients and 1 caregiver) responded to a survey interview conducted via telephone from August to September 2022. Of the 4 patients with lung cancer, 3 had experience with sotorasib; 1 patient with a KRAS G12C-mutated lung cancer had no experience with sotorasib. All respondents were female. All but 1 respondent (US) were from Canada (Nova Scotia, British Columbia, Quebec, Ontario).

From the submitted input, 1 patient said they felt "rock bottom" when the lung cancer progressed on chemotherapy and radiation, which led to being on oxygen along with acquiring a debilitating cough, shortness of breath from eating or talking and requiring assistance to shower. Another patient detailed the mental and emotional side effects associated with multiple courses of immunotherapy and chemotherapy, such as depression, anxiety, panic attacks, and severe mood swings, which remained debilitating even while in remission. The sole caregiver interviewed stated that it is mentally, physically, and financially challenging to care for a patient with lung cancer with comorbidities (e.g., preparing meals, making arrangements for transportation to medical appointments, managing daily responsibilities) and that they felt burned out without a lot of sources of support. Three patients with experience with sotorasib reported significant tumour reduction, that is, 50% to 65% to no evidence of disease within 5 weeks to 1.5 years. These patients reported that they experienced mild side effects, for example, fatigue, aches and pains when walking for

extended periods, a small or minor rash, diarrhea, shortness of breath, and increased liver enzymes while on sotorasib. However, the patients noted that these side effects did not have much impact on their daily activities and/or quality of life. According to input, these patients felt hopeful again that they could plan for the future.

Regarding key outcomes important to patients, 1 patient said they are most interested in a cure while maintaining a good quality of life. Respondents from the survey also expressed that they hoped a new treatment would provide an additional treatment option with an oral route of administration and accessibility from home, delay the onset of symptoms, prolong life, and improve functionality and mobility, with reduced side effects. The caregiver expressed the importance of treatment that can be accessed from home, limiting the need to travel to infusion clinics. Lastly, it was pointed out in the survey that waiting for lung surgeries across Canada is unacceptable, especially when patients and caregivers would like to treat lung cancer in the early stages. The caregivers surveyed said that wait time for the surgery was the most difficult part or the most challenging adverse effect related to the current treatment.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical experts, the treatment options for patients with KRAS G12C-mutated NSCLC who have progressed on standard therapy are limited. This patient population has an unmet need for an efficacious treatment associated with fewer AEs. The clinical experts consulted by CADTH for this review anticipated that sotorasib would be used following immunotherapy and platinum-doublet chemotherapy. Accordingly, docetaxel would then move to be either third or fourth-line therapy. The clinical experts consulted by CADTH noted that sotorasib would not be combined with other drugs. The clinical experts suggested that sotorasib be limited to patients with KRAS G12C-mutated NSCLC. Moreover, the clinical experts noted that treatment with sotorasib would not be suitable for patients with an Eastern Cooperative Oncology Group (ECOG) score of 3 or 4, with severe organ dysfunction, and for those with untreated symptomatic brain metastasis. The clinical experts did note that patients with untreated, asymptomatic brain lesions may be suitable for sotorasib; ideally, these patients should have their cases discussed at a multidisciplinary tumour board round at a centre with expertise in Stereotactic Radiosurgery. Based on input from the clinical experts, patients should undergo clinical and toxicity assessment per cycle (typically every 3 to 4 weeks) and imaging every 3 months to assess response to treatment in clinical practice. Based on input from the clinical experts, improved PFS and OS, and maintenance or improvement in quality of life are considered meaningful response to treatment in this population. The clinical experts suggested that treatment with sotorasib should be discontinued under the following 3 scenarios: patient decision to stop treatment with sotorasib; unacceptable toxicity due to sotorasib; and disease progression without clinical benefits. The clinical experts agreed that patients with documented disease progression could continue sotorasib if they were deriving clinical benefit. The clinical experts noted that sotorasib may be prescribed by a medical oncologist in an outpatient oncology clinical setting.

Clinician Group Input

Clinician group input was provided by Ontario Health – Cancer Care Ontario (OH-CCO)'s Lung Cancer Drug Advisory Committee (LC DAC), which consisted of input from 3 clinicians who had joint discussion via email; and LCC, which was based on a review of the literature and meeting proceedings from recent conferences compiled by 26 clinicians. Both clinician groups identified the following goals of therapy: reducing tumour burden; improving symptoms; and prolonging life while upholding patients' values and desires. Both clinician groups also noted that all patients eventually progress on currently available treatment; thus, durability of response is also an important treatment goal. In addition, LCC added the need for treatment associated with reduced toxicity and resource utilization. Indeed, OH-CCO LC DAC endorsed an oral anticancer treatment without the side effects and life impacts associated with chemotherapy to slow disease progress and ideally improve length and quality of life. According to input from OH-CCO LC DAC, sotorasib would be placed as second- or third-line monotherapy for patients who have progressed or are unable to tolerate platinum-based chemotherapy and immunotherapy (where appropriate) and possibly docetaxel. The OH-CCO LC DAC clinician group stated that sotorasib would not impact immunotherapy or doublet platinum chemotherapy use; however, sotorasib may be preferred to docetaxel if it can demonstrate a meaningful improvement in survival or quality of life since docetaxel has proven a survival benefit compared to best supportive care (BSC) and other chemotherapy regimens (ifosfamide), albeit with an unfavourable side effect profile. Input from LCC places sotorasib as the second-line standard of care for patients with advanced KRAS G12C NSCLC and suggests that sotorasib be used as a single drug after failing at least 1 line of prior systemic treatment. Based on input from both clinician groups, patients with a KRAS G12C- advanced NSCLC (stage IV or recurrent) who received prior therapy would be best suited for sotorasib. The LCC added that it is uncertain whether patients with ECOG performance status of 3 or 4 would benefit from treatment with sotorasib. Both clinician groups noted that patients eligible for treatment with sotorasib should be identified by a validated molecular diagnostic test, preferably next-generation sequencing. Both clinician groups noted that symptom improvement, stable disease, tumour shrinkage, radiographic reduction of disease site from baseline, and prolonged survival indicate a clinically meaningful response to treatment. The OH-CCO LC DAC added that the definition of a clinically meaningful improvement in the frequency or severity of symptoms depends on patients and varies across physicians. Based on input from LCC, response to treatment should be determined by the treating physician based on CT imaging and assessed every 2 to 3 months, similar to other oral tyrosine kinase inhibitors used in Canada. Based on input from the clinician groups, discontinuing treatment with sotorasib should be considered in the event of loss of clinical benefit as indicated by unequivocal disease progression (symptoms, poly-progression, and so forth.) or intolerable side effects. The LCC noted that treatment with sotorasib may continue in patients with disease progression that are oligoprogression amenable to local therapy (radiation or surgery), newly diagnosed or progression of brain metastases that have been treated with brain radiation or surgery, and asymptomatic diseases (without overt progression on imaging that are associated with increased symptom burden). The OH-CCO LC DAC emphasized that a combination of clinical judgment, radiological interpretation, and clinically standardized scales such as the Edmonton Symptom Assessment System should be used to determine if a patient is benefiting from therapy. The OH-CCO-LC also noted that the Response Evaluation Criteria in Solid Tumors (RECIST) and its derivatives are designed for clinical trials, not clinical practice, and should not be used to

determine treatment discontinuation. Both clinician groups agreed that an outpatient clinic would be an appropriate treatment setting for sotorasib in addition to the hospital setting. Both groups stated that a medical oncologist, general practitioner in oncology under medical oncology supervision, or respirologist experienced in treating patients with lung cancers should be involved in diagnosing, treating, and monitoring patients on sotorasib.

Drug Program Input

Input was obtained from the drug programs participating in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for sotorasib:

- considerations for prescribing of therapy
- care provision issues
- system and economic issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two sponsor-conducted studies were included in this systematic review: CodeBreaK 100, the pivotal trial, and CodeBreaK 200. CodeBreaK 100 is an ongoing, multicentre, noncomparative, open-label, single-group phase I/II study. phase I of CodeBreaK 100 was a dose exploration (part 1) and dose expansion (part 2) study aimed at evaluating the safety, tolerability, PK and pharmacodynamics of sotorasib in adult patients with KRAS G12C-mutated advanced NSCLC, colorectal cancer and other solid tumours.[19] Phase II of CodeBreaK 100 was designed to evaluate the efficacy and safety of sotorasib as monotherapy in adult patients with KRAS G12C-mutated advanced NSCLC, colorectal cancer, and other solid tumours.[20] CADTH's review of CodeBreaK 100 focuses on the phase II efficacy and safety results in adult patients with KRAS G12C-mutated advanced NSCLC. Phase II of CodeBreaK 100 enrolled 224 patients with KRAS G12C-mutated advanced solid tumours across 59 sites. Of the patients enrolled, 126 (56.3%) had NSCLC. Patients self-administered sotorasib 960 mg (8 × 120 mg tablets) orally once daily and continued treatment without interruption until disease progression, treatment intolerance, withdrawal of consent or death. Tumour response was assessed via contrast-enhanced CT (CT) or MRI (MRI) and assessed per RECIST version 1.1 by blinded independent central review (BICR). Patients underwent a safety follow-up visit 30 days (+ 7 days) after the last dose of sotorasib before any new anticancer treatment was started. Following safety follow-up visits, patients were followed long-term for health condition, disease status, and subsequent anticancer treatment every 12 weeks (± 2 weeks) up to 3 years after the last patient was enrolled or until withdrawal of consent, loss to follow-up or patient death, or whichever first occurred. The study team was blinded to

the efficacy data. The primary efficacy end point for phase II of CodeBreaK 100 was ORR, a composite of complete response (CR) and partial response. ORR was assessed by BICR. Secondary efficacy end points included duration of response (DOR), disease control rate (DCR), time to response (TTR), PFS, OS, and the NSCLC Symptom Assessment Questionnaire. Exploratory outcomes included changes in patient-reported cancer-specific symptoms and HRQoL measures, including the European Organization for Research and Treatment Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the lung cancer module (EORTC QLQ-LC13), the EQ-5D-5L and its Visual Analogue Scale (VAS), the question "I am bothered by the side effects of treatment" (GP5) of the Functional Assessment of Cancer Therapy – General (FACT-G), the patient global impression of change (PGIS) and severity (PGIS) questionnaires, and the patient-reported outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). The data cut-off for the primary analysis of phase II was September 1, 2020, which was updated at the data cut-off date of March 15, 2022. The updated data cut-off for OS at 2 years was September 9, 2022.

Patients enrolled in CodeBreaK 100 had a mean age of 62.9 (standard deviation [SD]: 9.3) years. Most patients were between the ages of 18 to 64 years (53.2%), white (81.7%), and former smokers (81%). Regarding disease characteristics, 61.9% and 98% of patients had stage IV disease at initial diagnosis and screening, respectively. At the time of screening, metastatic disease was identified in 96.8% of enrolled patients, with the most common site of metastasis found in the bone (48.4%). The most common histology type among enrolled patients was nonsquamous adenocarcinoma (95.2%). A total of 42.9%, 34.9% and 22.2% of patients received 1, 2, or 3 lines of prior lines of anticancer therapy, respectively. The most common types of prior anticancer therapy were immunotherapy checkpoint inhibitors (92.1%) and chemotherapy (91.3%). A total of 81% of patients received both platinum-based chemotherapy and anti-PD-1 or anti-PD-L1 immunotherapy.

CodeBreaK 200 is an ongoing, multicentre (148 sites across 22 countries), randomized (1:1), open-label, parallel-group, phase III study evaluating the efficacy of oral sotorasib (960 mg daily) (n = 171) versus IV docetaxel (75 mg/m^2 every 3 weeks) (n = 174) in adult patients with KRAS G12C-mutated NSCLC who progressed after prior platinum-based chemotherapy and a checkpoint inhibitor. Randomization was stratified by the following factors (as reported in the trial); number of prior lines of therapy in advanced disease (1 versus 2 versus > 2), race (Asian versus non-Asian) and history of central nervous system involvement (present or absent). Patients continued treatment without interruption until disease progression, treatment intolerance, withdrawal of consent, or death. Tumour response was assessed via contrast-enhanced CT or MRI and assessed per RECIST 1.1 by a BICR every 6 weeks from cycle 1, day 1 until week 49, and then at 9-week intervals thereafter. A cycle was defined as 21 days in length + 3 days unless a delay was medically necessary. Patients randomized to the docetaxel treatment group who experienced disease progression, confirmed by radiological assessment after study initiation, were permitted to crossover to the sotorasib treatment group. The primary end point of CodeBreaK 200 was PFS. Key secondary end points included OS, ORR, and HRQoL as assessed by the EORTC QLQ-30 and QLQ 13. Other secondary end points included DOR, TTR, and DCR. The data cut-off date of the primary analysis was August 2, 2022.

Patients randomized in CodeBreaK 200 had a mean age of 63.5 (SD, 9.5) years. Most patients were between the ages of 18 to 64 years (53.9%), white (82.9%) and current or former smokers (96.2%). With disease

characteristics, metastatic disease was identified in 95.1% of randomized patients. The most common histology type among the randomized patients was nonsquamous (96.8%). A total of 42.9%, 40.9%, and 16.2% of patients received 1, 2, or 3, or more complete prior lines of therapies, respectively; and 34.2% were on maintenance therapy. Between the 2 treatment arms, a greater proportion of patients were males in the sotorasib (63.7%) relative to the docetaxel (54.6%) treatment group. Other imbalance in baseline characteristics between the sotorasib and docetaxel treatment groups were noted for the following: PD-L1 protein expression of at least 1% and less than 50% (sotorasib, 26.9%; docetaxel, 40.2%); ECOG status 0 at cycle 1 day 1 (sotorasib, 38.6%; docetaxel, 33.9%) and best response to prior treatment of primary refractory (sotorasib, 39.2%; docetaxel, 32.8%) and initial response with subsequent growth (sotorasib, 20.5%; docetaxel, 27.0%)

Baseline patient characteristics were generally similar between CodeBreaK 100 and CodeBreaK 200.

Efficacy Results

In CodeBreaK 200, the Maurer-Bretz multiple testing procedure was used to control the study-level overall type I error rate below 1-sided 0.025 levels, starting with PFS. If all 3 hypotheses of PFS, ORR, and OS, were sequentially rejected, then the end points of change from baseline over 12 weeks for the symptoms of dyspnea, cough, and pain as measured by the QLQ-C30 and QLQ-LC13 would be tested using Holm's procedure. The key secondary HRQoL outcomes assessed in CodeBreaK 200 were not statistically tested since the hierarchical testing was stopped at the nonstatistically significant OS end point.

Overall Survival

In CodeBreaK 100, the proportion of observed deaths at the time of primary data cut-off (September 1, 2020) was 38.1%. The median OS was 12.0 (95% CI, 9.5 to not evaluable [NE]) months. The probability of survival based on Kaplan-Meier (KM) estimates at 3, 6, 9, and 12 months were 89.5% (95% CI, 82.7 to 93.8), 75.5% (95% CI, 66.8 to 82.2), 63.4% (95% CI, 53.8 to 71.5) and 51.6% (95% CI, 36.7 to 64.5), respectively. Results for OS at the updated analysis with data cut-off date March 15, 2021, were generally consistent with the results from the primary data cut-off date with median OS of 12.5 (95% CI, 10.0 to NE) months. The results for OS at 2 years, with data cut-off date of September 9, 2022, was consistent with the results from the previous data cut-off dates with a median OS of 12.48 (95% CI, 9.99 to 19.29). The probability of survival based on KM estimates at 18 and 24 months were 42.08% (95% CI, 32.97 to 50.90%) and 31.56% (95% CI, 23.15 to 40.29%), respectively.

In CodeBreaK 200, the proportion of observed deaths at the time of data cut-off (August 2, 2022) was 63.7% and 54.0% in the sotorasib and docetaxel treatment arms, respectively. The median OS was 10.64 (95% CI, 8.94 to 13.96) months in the sotorasib group and 11.3 (95% CI, 9.00 to 14.85) months in the docetaxel group. The stratified HR for OS was 1.01 (95% CI, 0.77 to 1.33; P = 0.53) following treatment with sotorasib versus docetaxel. In total, 59 patients randomized to docetaxel crossed over to receive treatment with sotorasib; crossover occurred in 46 patients following disease progression (per-protocol) while 13 patients received sotorasib as subsequent treatment upon disease progression. The results of the sensitivity analyses exploring the crossover effect on OS in CodeBreaK 200 were consistent with the main analysis. In the analyses based on patients who were per-protocol crossovers, the HR (95% CI) for survival was 1.01 (0.66

to 1.49) in the rank preserving structural failure time analysis, 0.99 (0.73 to 1.34) in the inverse probability of censoring weighting adjusted analysis and 0.885 (0.17 to 1.33) in the two-stage approach adjusted analysis. Sensitivity analysis of OS exploring the crossover effect among all 59 crossover patients using the two-stage approach resulted in HR (95% CI) for survival of 0.82 (0.14 to 1.33).

Progression-Free Survival

In CodeBreaK 100, 56.9% experienced progression or death due to any cause at the time of the September 2020 data cut-off. The median PFS was 6.7 (95% CI, 4.9 to 8.1) months. The probability of PFS at 3, 6, and 9 months was 67.5% (95% CI, 58.2% to 75.2%), 51.5% (95% CI, 41.9% to 60.4%), and 36.2% (95% CI, 26.7 to 45.8%), respectively. Sensitivity analysis for PFS using investigator's assessment were consistent with the results obtained by BICR. At the time of the March 2021 data cut-off, 70.2% of patients had experienced progression or death due to any cause. Median PFS was consistent with the earlier data cut-off (6.8 months; 95% CI, 5.1 to 8.2 months).

Among patients in CodeBreaK 200, disease progression or death on or before the data cut-off date was observed in 71.3% of patients in the sotorasib treatment group and in 58.0% of patients in the docetaxel group. The median PFS was 5.62 (95% CI, 4.27 to 7.75) months in the sotorasib group and 4.47 (95% CI, 3.02 to 5.68) months in the docetaxel group at the time of data cut-off. The stratified HR for disease progression or death was 0.66 (95%, 0.51 to 0.86, P = 0.002) in favour of sotorasib versus docetaxel. Sensitivity analysis for PFS using investigator's assessment were consistent with the results obtained by BICR.

Patient-Reported Outcomes

EORTC QLQ-C30

In CodeBreaK 100, 98 (78%) patients completed the EORTC QLQ-C30 at baseline. The number of patients available for completing the measure diminished consistently with each cycle. At the end of treatment, 38 (43.2%) patients completed the assessment. Over time, scores for both global health status and physical functioning appeared to remain relatively stable. Change from baseline in global health status ranged from −5.33 (SD: 15.57) (cycle 11, n = 25) to + 1.37 (SD: 19.44) (cycle 5, n = 61). Change from baseline in physical functioning ranged from −8.57 (SD: 20.33) (cycle 13, n = 14) to + 6.67 (SD: 22.05) (cycle 7, n = 33).

In CodeBreaK 200, the baseline EORTC QLQ-C30 was completed by 168 (98.2%) and 158 (90.8%) patients in the sotorasib and docetaxel treatment arms, respectively. Compliance rates for the questionnaire remained consistently high, above 90%. The number of patients available for completing the measure diminished consistently with each cycle. At cycle 5 day 1 (week 12), the EORTC QLQ-C30 was completed by 69 (39.7%) patients in the docetaxel treatment group and by 106 (62.0%) patients in the sotorasib treatment group. The difference between groups in the least square change from baseline to week 12 for global health status was 6.93 (95% CI, 3.66 to 10.19) and for physical functioning was 8.78 (95% CI, 5.39 to 12.17), favouring treatment with sotorasib (n = 106) relative to docetaxel (n = 69).

EQ-5D-5L and VAS

In CodeBreaK 100 the EQ-5D-5L remained relatively stable during the treatment period. At baseline (n = 86), most patients (68% to 94%) reported that they had no problems or slight problems with the dimensions of

health assessed by the EQ-5D-5L. At the end of the treatment phase (n = 28; 22.2%) 42.9% and 21.4% of patients reported that they had no problems or slight problems. The VAS scores remained relatively stable during the treatment period. The mean VAS score at baseline was 70.2 (SD, 17.5; n = 86), indicating patients generally rated their health favourably (with a score of 100 indicative of best health imaginable). Change in mean score from baseline over the treatment period ranged from −24.0 (SD, 32.8; cycle 15, n = 4) to 2.7 (SD, 18.6; cycle 3, n = 69; and SD, 16.6; cycle 7, n = 31). By the end of the treatment phase, the mean VAS score was 61.5 (SD, 19.5; n = 28), which was associated with a mean change from baseline of −10.6 (SD, 19.3). For both the EQ-5D-5L and the VAS, the number of patients providing assessments had dropped to less than 50% after cycle 6 in CodeBreaK 100.

In CodeBreaK 200, baseline EQ-5D-5L was completed by 160 (93.6%) patients in the sotorasib treatment group and by 138 (79.3%) patients in the docetaxel treatment group. The number of patients available for completing the measure diminished consistently with each cycle. At cycle 5 day 1, the EQ-5D-5L was completed by 105 (61.4%) patients in the sotorasib treatment group and 67 (38.5%) patients in the docetaxel treatment group. At baseline, most patients in both the sotorasib (64.4% to 93.2%) and docetaxel (69.6% to 90.6%) treatment arms reported that they had no problems or slight problems with the dimensions of health assessed by the EQ-5D-5L. At cycle 5, day 1, 79.0% to 96.2% of patients in the sotorasib treatment group and 61.2% to 85.1% of patients in the docetaxel treatment group reported no problems or slight problems. Between-group differences for change from baseline on EQ-5D-5L scales were not reported. Baseline VAS – a secondary outcome – was completed by 166 (97.1%) and 154 (88.5%) patients in the sotorasib and docetaxel treatment groups, respectively. Compliance rates for this measure were consistently > 80%. The number of patients available for completing the measure diminished consistently with each cycle. At cycle 5 day 1, the VAS was completed by 106 (62.0%) patients in the sotorasib group and 69 (39.7%) patients in the docetaxel group. At baseline, mean VAS scores were 67.6 (SD, 19.9) and 68.3 (SD, 20.3) in the sotorasib and docetaxel treatment groups, respectively. At cycle 5 day 1, mean VAS score for patients in the sotorasib treatment group was 73.2 (SD, 18.6) which was associated with a mean change from baseline of 2.2 (SD, 15.5) for sotorasib. For patients in the docetaxel treatment group (n = 67), the mean VAS score at cycle 5 day 1 was 67.7 (SD, 20.8), which was associated with a mean change from baseline of −5.8 (SD, 18.2). Between-group differences for change from baseline on the VAS were not reported.

EORTC QLQ-C30 symptom scales

In CodeBreaK 100, baseline EORTC QLQ-C30 symptom scores were completed by 94 (76.4%) patients. The number of patients available for completing the measure diminished consistently with each cycle. After cycle 6, the number of patients providing assessments had dropped to less than 50%. From baseline (n = 94) to the end of the treatment phase of the study (n = 32), mean scores were sustained for diarrhea (no change) and dyspnea (mean change from baseline 3.13 [SD, 39.1]). The symptom score for fatigue, nausea/vomiting, and pain increased during the study period.

In CodeBreaK 200, the dyspnea subscale was considered the most important symptom, and the only symptom-specific scale of the EORTC QLQ-C30 reported. At cycle 2 day 1, a total of 148 (86.5%) patients in the sotorasib treatment group and 112 (64.4%) patients in the docetaxel treatment group completed the

dyspnea subscale. At cycle 5 day 1, the proportion of patients available to complete the dyspnea subscale of the EORTC QLQ-C30 was 61.4% and 38.5% of patients in the sotorasib and docetaxel treatment groups, respectively. The difference between groups in the least square change from baseline for dyspnea at week 12 was −10.09 (95% CI, −13.39 to −6.78), favouring treatment with sotorasib (n = 105) relative to docetaxel (n = 67).

EORTC QLQ-LC13 symptom scales

The 3 main symptoms of lung cancer are dyspnea, cough, and chest pain and thus were the focus of the assessment. In CodeBreaK 100 the least square mean scores were maintained or decreased over time for the EORTC QLQ-LC13 subscales of dyspnea, cough, and chest pain from baseline (n = 86) to the end of the treatment phase at cycle 17 (n = 28). The least square mean changes from baseline ranged from −11.2 (95% CI, −16.2 to −6.1; cycle 2, n = 77) to −7.1 (95% CI, −13.2 to −1.1; cycle 6, n = 45) for cough; −4.9 (95% CI, −10.3 to 0.4; cycle 7, n = 31) to −0.44 (95% CI, −5.12 to 4.24; cycle 6, n = 45) for chest pain; and −3.4 (95% CI, −7.8 to 1.0; cycle 4, n = 58) to −0.14 (95% CI, −5.7 to 5.41; cycle 9, n = 25) for dyspnea. After cycle 6, the number of patients providing assessments had dropped to less than 50%.

In CodeBreaK 200, the dyspnea, cough, and chest pain subscales of the EORTC QLQ-LC13 were completed at baseline by 166 (97.1%) and 154 (88.5%) patients in the sotorasib and docetaxel treatment arms, respectively. Compliance rates were consistently high, mostly above 90%. The number of patients who completed the EOTRC QLQ-LC13 at cycle 5 day 1 (week 12) in the sotorasib and docetaxel treatment groups was 106 (62.0%) and 69 (39.7%), respectively. The total number of patients available to provide assessments dropped below 50% at cycle 6 day 1. The odds of improved symptoms at week 12 favoured sotorasib relative to docetaxel for cough (OR, 3.21; 95% CI, 1.55 to 6.65) and dyspnea (OR, 3.58; 95% CI, 1.98 to 6.46). The odds of improved chest pain at week 12 for sotorasib compared to docetaxel was 1.56 (95% CI, 0.82 to 2.96).

Objective Response Rate

In CodeBreaK 100, 1.6% of patients were documented as having CR to sotorasib, while 35.8% had partial response (PR) to treatment at the time of the September 2020 data cut-off. The ORR (CR + PR) was 37.4% (95% CI, 28.84% to 46.58%). The study achieved the predetermined threshold for a positive outcome (lower limit of the 95% CI for ORR > 23%). The mean time to objective response was 1.95 months (SD, 1.23 months). At the time of the March 2021 data cut-off, 3.2% of patients were documented as having CR, while 33.9% had PR. The ORR (CR + PR) was consistent with the earlier data cut-off (37.1%; 95% CI, 28.60% to 46.23%). The mean time to objective response, as observed in the updated analysis, was 2.11 (SD, 1.71) months.

In CodeBreaK 200, the proportion of patients documented as having an objective response (CR or PR) to treatment at the time of data cut-off in the sotorasib and docetaxel groups were 28.1% (95% CI, 21.5 to 35.4) and 13.2% (95% CI, 8.6 to 19.2), respectively; resulting in a difference in proportion of 14.8% (95% CI, 6.4 to 23.1; P < 0.001) in favour of sotorasib. The odds of objective response were higher among patients randomized to the sotorasib group relative to those randomized to docetaxel (OR, 2.6; 95% CI, 1.48 to 4.56, P < 0.001). The mean time to objective response as of the August 2, 2022, data cut-off date was 2.43 (SD, 1.80) months among patients in the sotorasib treatment group and 3.24 (SD, 2.08) months in the docetaxel treatment group. Of note, there was an imbalance across groups in the proportion of patients for whom

response assessments were not done (5.8% and 24.1% of patients in the sotorasib and docetaxel groups, respectively).

Duration of Response

In CodeBreaK 100, a DOR of at least 3 months and of at least 6 months was documented in 76.1% and 50.0% of patients, respectively, at the primary data cut-off (1 September 2020). The median DOR was 8.4 (95% CI, 6.9 to 8.4) months. The probability of response based on KM estimates at 3 and 6 months were 89.9% (95% CI, 75.3% to 96.1%) and 76.2% (95% CI, 59.1 to 86.9), respectively. Results for DOR at the updated analysis with data cut-off date 15 March 2021 were overall consistent with the results from the primary data cut-off, with a DOR of at least 3 months and at least 6 months documented in 82.6% and 60.9% of patients, respectively. The median DOR was 11.1 (95% CI, 6.9 to NE) months and the probability of objective response based on KM estimates at 3 and 6 months were 90.5% (95% CI, 76.7 to 96.3) and 70.8% (95% CI, 54.3 to 82.2), respectively. At 9 and 12 months, the probabilities of objective response were 57.3% (95% CI, 40.4 to 71.0) and 48.2% (95% CI, 31.5 to 63.0), respectively.

In CodeBreaK 200, the proportion of patients with a DOR of at least 3- and 6 months was not available to the CADTH review team. The median DOR based on BICR of disease response per RECIST v1.1 was 8.64 (95% CI, 7.06 to 17.97) months and 6.80 (4.27 to 8.28) months in the sotorasib and docetaxel treatment arms, respectively.

Harms Results

Adverse Events

At the September 1, 2020 data cut-off date in CodeBreaK 100, a total of 125 (99.2%) patients in the NSCLC cohort had AEs. Overall, 75 (59.5%) patients had grade 3 or worse AEs, and 21 (16.1%) patients had a grade 4 or worse AE. The 3 most common AEs reported were diarrhea (49.2%), nausea (29.4%), and fatigue (25.4%). Reported AEs at the subsequent updated analysis with data cut-off date 15 March 2021 were overall consistent with those from the primary data analysis. At the time of the updated analysis, 125 (99.2%) patients reported at least 1 AE; of which 77 (61.1%) had grade 3 or worse AE and 24 (19.0%) had grade 4 or worse AE. The 3 most common AEs reported at the time of the updated analysis were diarrhea (50.8%), nausea (31.0%) and fatigue (21.4%).

In CodeBreaK 200, 98% of patients in the sotorasib and docetaxel treatment arms reported at least 1 AE. The most common AEs reported in the sotorasib treatment group were diarrhea (41.4%), nausea (26.0%) and decreased appetite (23.1%). The most common AEs reported in the docetaxel treatment group were fatigue (29.8%), diarrhea (25.8%), and nausea (25.8%). Alopecia occurred in 3 (1.8%) of patients in the sotorasib group and 35 (23.2%) in the docetaxel group. Grade 3 or worse AEs were reported by 121 (71.6%) patients in the sotorasib treatment group and in 91 (60.3%) patients in the docetaxel treatment group. Grade 4 or worse AEs were reported in 48 (28.4%) and 35 (23.2%) patients in the sotorasib and docetaxel treatment arms, respectively. The most common grade 3 or worse AEs in the sotorasib treatment group were diarrhea (13.6%), NSCLC (10.1%), alanine aminotransferase (ALT) increased (8.3%), and aspartate aminotransferase (AST) increased (5.9%). In the docetaxel treatment group, the most common grade 3 or worse AEs were neutropenia (8.6%), anemia (6.6%), fatigue (6.0%), pneumonia (6.0%) and febrile neutropenia (5.3%)

Serious Adverse Events

In CodeBreaK 100, a total of 63 (50%) patients in the NSCLC cohort of CodeBreaK 100 had at least 1 serious adverse event (SAE) at the time of primary data analysis (September 1, 2020). Of those patients reporting SAE, 60 (47.6%) had a grade 3 or worse AEs and 19 (15.1%) had a grade 4 or worse AE. The most frequently reported SAEs were pneumonia (7.1%), pleural effusion (4.8%), and back pain (3.2%). SAEs at the time of the subsequent updated analysis with cut-off date 15 March 2021 were documented in 69 (54.8%) of patients. The grade of SAEs at the time of the updated analysis was not available to the CADTH review team. The most frequently reported SAEs at the time of the updated analysis were pneumonia (7.1%), NSCLC (6.3%) and pleural effusion (4.0%).

In CodeBreaK 200, SAEs were reported by 91 (53.8%) patients in the sotorasib treatment group and 67 (44.4%) patients in the docetaxel treatment group. The most frequently reported SAE in the sotorasib treatment group was NSCLC (10.7%). The most frequently reported SAEs in the docetaxel treatment group were pneumonia (6.6%) followed by febrile neutropenia (4.6%), NSCLC (3.3%), and anemia (3.3%)

Withdrawal Due to AEs

A total of 11 (8.7%) patients in the NSCLC cohort of CodeBreaK 100 discontinued treatment due to AEs at the time of primary data analysis (September 1, 2020) and subsequent updated analysis (15 March 2022). The most common reasons for treatment discontinuation were drug-induced liver injury (2.4%), alanine aminotransferase (ALT) increased (1.6%), aspartate aminotransferase (AST) increased (1.6%) and pneumonitis (1.6%) at the time of both primary and subsequent updated analysis.

In CodeBreaK 200, 28 (16.6%) and 24 (15.9%) patients discontinued treatment due to an AE in the sotorasib and docetaxel treatment group, respectively. Reasons for discontinuing treatment in the sotorasib treatment group included ALT increased (3.6%), NSCLC (3.0%), blood bilirubin increased (2.4%), AST increased (1.2%), asthenia (1.2%) and blood alkaline phosphatase (ALP) increased (1.2%). In the docetaxel treatment group, reasons for discontinuing treatment included fatigue (2.0%), NSCLC (1.3%), anemia (1.3%), febrile neutropenia (1.3%), pneumonitis (0.7%), and asthenia (0.7%).

Dose Modification Due to AEs

In CodeBreaK 100, a total of 48 (38.1%) and 22 (17.5%) patients required dose modification of sotorasib due to AE at the time of the primary data analysis (1 September 2020) and subsequent updated analysis (March 15, 2021), respectively. Reasons for dose modification were consistent at both data analysis points. The most common reasons for dose modification due to AE were diarrhea (8.7%), AST increased (8.7%), ALT increased (8.7%), and blood ALP increased (4.0%).

In CodeBreaK 200, dose modification due to AEs were required by 26 (15.4%) and 43 (28.5%) patients in the sotorasib and docetaxel treatment arms, respectively. The most frequently reported reason for dose modification in the sotorasib treatment group was diarrhea (8.3%), followed by ALT increased (3.6%), AST increased (1.8%) and blood ALP increased (0.6%). In the docetaxel treatment group, the most frequently reported reasons for dose modification were neutropenia (4.6%) and fatigue (4.0%) followed by asthenia (3.3%) and diarrhea (2.0%).

Dose Interruption

In CodeBreaK 100, dose interruption due to AEs were documented in 46 (36.5%) patients at the time of the March 15, 2021, data cut-off date.

In CodeBreaK 200, dose interruption due to AEs were reported in 85 (50.9%) patients in the sotorasib treatment group and in 42 (27.8%) patients in the docetaxel treatment group. Most frequently reported reasons for dose interruption in the sotorasib treatment group were diarrhea (15.4%), ALT increased (5.9%), AST increased (5.3%), nausea (4.7%), decreased appetite (3.0%) and fatigue (1.2%). In the docetaxel treatment group, dose interruptions were due to pneumonia (4.6%), fatigue (3.3%) and nausea (0.7%).

Mortality

At the time of the primary data analysis at data cut-off (September 1, 2020) in CodeBreaK 100, 18 (14.3%) patients died due to an AE. At the time of the subsequent updated analysis (March 15, 2021), 20 (15.9%) patients died due to an AE by the time of the updated analysis. None of the deaths were considered attributable to treatment-related AEs.

In CodeBreaK 200, fatal AEs were recorded in 37 (21.9%) patients in the sotorasib treatment group and in 18 (11.9%) patients in the docetaxel treatment group. Seventeen (10.1%) patients in the sotorasib treatment group and 5 (3.3%) patients in the docetaxel group experienced fatal AEs related to NSCLC disease progression.

Notable Harms

At the time of CodeBreaK 100 primary data analysis with the data cut-off date of September 1, 2020, a total of 40 (31.7%) patients in the NSCLC cohort reported hepatotoxicity, with the most common events documented as AST increased (21.4%), ALT increased (20.6%), and blood ALP increased (13.5%). Renal toxicity was reported in 21 (16.7%) patients in NSCLC cohort and included hyponatremia (5.6%) and hypoalbuminemia (3.2%), hyperkaliemia (2.4%), hypocalcemia (2.4%) and hypophosphatemia (1.6%), and blood creatine increased (0.8%). There were no documented cases of interstitial lung disease. Pneumonitis was reported in 3 (2.4%) patients in the NSCLC cohort. Peripheral neuropathy was reported in 1 (0.8%) patient in the NSCLC cohort. Lastly, GI toxicity was reported in 93 (73.8%) patients in the NSCLC cohort and included diarrhea (49.2%), nausea (29.4%), and vomiting (18.3%). Reported notable harms at the subsequent updated analysis with data cut-off date March 15, 2021, were overall consistent with those from the primary data analysis. At the updated data analysis, March 15, 2021, a total of 40 (31.7%) patients reported hepatoxicity with the most common documented as AST increased (21.4%), ALT increased (20.6%), and blood ALP increased (13.5%). Renal toxicity was reported in 23 (18.3%) patients and included hyponatremia (7.1%), hypoalbuminemia (3.2%), blood creatine increased (0.8%), hyperkaliemia (2.4%), hypocalcemia (3.2%), and hypophosphatemia (2.4%). There were no documented cases of interstitial lung disease at the time of the updated analysis. Pneumonitis was reported in 3 (2.4%) patients in the NSCLC cohort in the updated analysis. Peripheral neuropathy was reported in 1 (0.8%) patient in the NSCLC cohort in the updated analysis. The overall number of patients with GI toxicity was not reported at the time of the subsequent updated analysis. The following notable AEs related to GI toxicity were reported: diarrhea (50.8%), nausea (31.0%), vomiting (18.3%), constipation (19.0%) and abdominal pain (8.7%).

In CodeBreaK 200, hepatoxicity AEs including AST increased (10.7%), ALT increased (10.7%), blood ALP increased (7.7%) and gamma glutamyltransferase increased (4.0%) were reported in the sotorasib treatment group while in the docetaxel treatment group 2% or less of patients reported hepatoxicity due to these reasons. Renal toxicity related to hyponatremia was reported in 8 (4.7%) patients in the sotorasib treatment group and in 4 (2.6%) patients in the docetaxel treatment group while hypoalbuminemia was reported in 4 (2.4%) patients in the sotorasib treatment group and 8 (5.3%) of patients in the docetaxel treatment group. Interstitial lung disease was reported in 1 patient in the sotorasib treatment group and pneumonitis was reported in 3 (1.8%) patients in the sotorasib treatment group and in 3 (2.0%) patients in the docetaxel treatment group. Peripheral neuropathy was documented in 1 (0.6%) patient in the sotorasib treatment group and in 16 (10.6%) patients in the docetaxel group. Notable GI toxicities reported in the sotorasib treatment group included diarrhea (41.4%), nausea (26.0%), vomiting (13.0%), constipation (13.0%) and abdominal pain (11.8%). Notable GI toxicities reported in the docetaxel treatment group included diarrhea (25.8%), nausea (24.5%), constipation (19.2%) and vomiting (9.9%).

Critical Appraisal

The single-group, open-label, nonrandomized, design of CodeBreaK 100 study makes interpretation of the efficacy and safety of sotorasib challenging. The lack of comparison with an active comparator, BSC, and/or placebo precludes the ability to draw causal inferences or assess the relative therapeutic benefits or safety of sotorasib. The risk of selection bias cannot be ruled out given the lack of transparency regarding the selection and timing of enrolment of patients into the trial. Interpretation of time-to-event end points such as OS and PFS is limited in single-group studies; since all patients with KRAS G12C-mutated advanced NSCLC received the same treatment, the extent to which the observed survival is due to the natural history of the tumour, or the intervention remains unclear. The CodeBreaK 100 trial included no formal statistical significance and hypothesis testing and point estimates with 95% Cis were reported to estimate the magnitude of treatment effect. To mitigate the limitations associated with open-label studies, tumour response and disease progression outcomes were blinded to the study investigator and were assessed by BICR. However, as noted by the FDA assessment on sotorasib, the analyses of PFS and OS are uninterpretable in the single-group study. The results for patient-reported outcomes were inconclusive, given the noncomparative, open-label design of the trial, and the substantial decline in the number of patients available to provide assessments over time. Due to the above-mentioned limitations, the ability to draw firm conclusion on the magnitude of clinical benefit and safety of sotorasib was limited. The results were found to be overall generalizable to the clinical setting by the clinical experts consulted by CADTH for the purpose of this review, although patients in the trial were judged to be younger and healthier (lower ECOG performance status) than patients typically seen in practice.

In CodeBreaK 200, patients were randomized centrally using interactive response technology, which is typically adequate for concealing allocation until treatment assignment. While the randomization stratification factors appear appropriate, several between-group imbalances at baseline suggested that prognostic balance may not have been achieved between groups. Of concern was the proportion of patients in the docetaxel treatment group who were randomized to but not dosed (13.2%), namely due to refusal of treatment, and discontinued the study by way of withdrawal of consent (22.4%). As a result, unequal

censoring between the sotorasib and docetaxel treatment arms was observed (e.g., a 10% difference in censoring between the groups for OS; 13% difference in censoring for PFS) introducing uncertainty about treatment effects. In addition, a sizable proportion of patients in the docetaxel treatment group (24%) had an outcome of "not measured" in the ORR analysis. The sponsor clarified that the majority of patients who did not have ORR measured did not received docetaxel because of withdrawal of consent or other reasons. The extent and direction of bias associated with the ORR analysis is uncertain. The risk of attrition bias cannot be ruled out due to the disproportionate loss of patients by way of self-withdrawal. There is added uncertainty for PFS rates measured over the study period due to the limited number of patients at risk by month 12. To minimize the risk of bias in the measurement of the outcomes associated with the open-label design, patients' responses to treatment were blinded to the study investigator, and tumour response was confirmed by radiologic evidence, and done by BICR as per RECIST 1.1. Sensitivity analysis of PFS and ORR demonstrated consistency between the BICR and investigator's assessment of tumour response, suggesting that the risk for bias in response outcomes from the open-label design is likely not substantial. CodeBreaK 200 assessed 2 measures of HRQoL and symptom burden – outcomes deemed important by patients and clinicians – as key secondary outcomes. However, the key secondary HRQoL outcomes were not statistically tested since the hierarchical testing was stopped at the nonstatistically significant OS end point. Furthermore, the open-label nature of CodeBreaK 200 increases the risk of bias in the measurement of the subjective HRQoL. Adding further uncertainty to the HRQoL and other symptom burden outcomes was some missing baseline data and the low completion rates in both the sotorasib and docetaxel treatment groups. In the docetaxel treatment group, after cycle 3, there were less than 50% of patients available to provide assessment for the QLQ-C30, the subscales of the QLQ-LC13 and the EQ-5D-5L. Consequently, there would be no reliable assessment for the docetaxel treatment group for HRQoL and symptom burden measures. The HRQoL and symptom burden outcomes are at high risk of attrition bias as long-term survivors tend to be the healthier patients. Analysis of efficacy results followed a defined statistical analysis plan, employed appropriate censoring criteria and accounted for patient crossover from the docetaxel to the sotorasib treatment group. Following recommendations from the FDA to reduce the number of patients exposed to docetaxel, the original sample size (powered for the primary end point of PFS and the secondary end point of OS) was reduced. As a result, the CodeBreaK 200 trial was still powered to detect a difference in PFS but no longer to detect a difference in OS. In addition, the protocol was amended to allow the crossover of patients in the docetaxel group to sotorasib upon centrally confirmed radiological disease progression. The sponsor conducted sensitivity analyses of OS that adjusted for the crossover effect. While the results of these analysis were consistent with the overall treatment effect; the CI were too wide to draw any conclusions of certainty with respect to whether sotorasib or docetaxel were favoured for OS.

Indirect Comparisons

At the time of initial submission to CADTH in August 2022, data from CodeBreaK 200 were not available. In the absence of direct comparative data between sotorasib and docetaxel from the CodeBreaK 200 trial, the sponsor submitted an indirect treatment comparison in the form of a matching-adjusted indirect comparison (MAIC) which was used to inform the pharmacoeconomic model. The unanchored MAIC estimated the comparative OS and PFS between sotorasib and docetaxel in patients with locally advanced or metastatic

NSCLC (stage IIB – IV) and confirmed KRAS mutation, in the absence of direct comparative evidence from a randomized trial. The MAIC was based on individual patient data from the single-group, open-label index trial CodeBreaK 100 and aggregate-level data from the docetaxel 75 mg/m^2 plus placebo group of the double-blinded, randomized SELECT-1 trial. In November 2022, this submission was temporarily suspended as the sponsor had informed CADTH that the economic evaluation would be revised to include data from CodeBreaK 200. In May 2023, the temporary suspension was lifted upon receipt of the revised economic model from the sponsor. After receiving data from CodeBreaK 200, which provided direct comparative evidence between sotorasib and docetaxel, the CADTH review team determined that the MAIC no longer addressed any gap in the evidence and therefore, the submitted MAIC was not included in the clinical report.

Other Relevant Evidence

This section summarizes the partial results of the global expanded access program (EAP). Although this study did not meet the systematic review inclusion criteria, it provides supportive evidence for patients with ECOG performance status of 2, which was a patient group excluded from CodeBreaK 100 and CodeBreaK 200. Furthermore, the clinical expert consulted by CADTH, and input received from clinician groups to this submission expressed desire for treating patients with ECOG PS 2. Input received from the clinician group, LCC, to this submission indicated that benefit in patients with ECOG PS 3 to 4 remains debatable. The CADTH review team summarized the study designs and data of the global EAP to provide supplemental evidence for decision-making.

The global EAP provided compassionate use of sotorasib before local regulatory approval. Patients eligible for the EAP were between the ages of 18 and 99 years with an ECOG performance status score equal or less than 2, and had pathologically documented, locally advanced and unresectable or metastatic KRAS^{G12C}-mutated NSCLC confirmed through molecular testing. Patients had to demonstrate that they had exhausted other standard-of-care options for locally advanced and unresectable or metastatic NSCLC disease, including platinum-based combination chemotherapy and PD 1/PD-L1 immunotherapy (unless medically contraindicated). Patients participating in any ongoing clinical study of sotorasib, with mixed small cell lung cancer or mixed NSCLC histology, active brain metastases, active hepatitis B or hepatitis C virus, current active malignancy other than NSCLC, and those previously enrolled in a prior sotorasib studies, were excluded from participating. The primary end points included safety (treatment-emergent adverse events [TEAEs], AEs of interest, SAEs, and so forth.). Key secondary end points included OS and treatment duration with real-world PFS as the ad hoc end point. The sponsor submitted abstract, poster, and presentation summarized the data from 2 global protocols under the EAP (Amgen study 20190236 [study-436] and 20190442 [study-442]) that evaluated the safety and efficacy of sotorasib outside the registrational trial setting in patients with advanced KRAS^{G12C}-mutated NSCLC in multiple countries (US, Spain, Argentina, Brazil, Israel, Saudi Arabia and Taiwan) and across 49 centres. Real-world PFS was estimated for Study-436 and was defined as time from start of treatment to end of protocol due to disease progression or death, any death before new anticancer therapy or end of commercial sotorasib, whichever occurred first.

A total of 147 patients received sotorasib 960 mg daily under the EAP – Study 436. The median number of prior lines of anticancer therapy reported by the patients before receiving sotorasib was 2 (up to 8) prior

lines. At baseline, a total of 25.2% of patients had an ECOG performance status score of 2, and 32.7% of patients had brain metastases.

Efficacy Results

Real-world PFS was estimated for the 92 patients enrolled in Study-436 of the global EAP study. The median real-world PFS as of the data cut-off date June 24, 2022, was 6.7 months (95% CI, 4.6 to 8.3 months) with 60 (65.2%) events. OS was estimated for 147 patients. The median OS as of data cut-off date November 8, 2022, was 9.5 months (95% CI, 8.6 to 12.0 months). The median real-world PFS was comparable to the PFS efficacy results reported in CodeBreaK 100 and CodeBreaK 200.

Harms Results

The global EAP study presented AEs as treatment-related AEs and thus were not reported by the CADTH review team.

Critical Appraisal

Lacking the details of the study methodology, the CADTH review team was unable to complete a robust critical appraisal of the internal and external validity of the study results. A key limitation to the global EAP study was the noncomparative design of the global EAP study and lack of statistical testing, which precluded causal conclusions. The study was open-label and the method for ascertaining PFS or OS was not reported, so the potential for and extent of any bias in the measurement of this outcome was unknown. Although the results were comparable to the PFS efficacy results reported in the CodeBreaK 100 and CodeBreaK 200 trials, the magnitude of the treatment effect for the real-world PFS should be interpreted with uncertainty in light of the aforementioned limitations. The study did not report on outcomes other than PFS and OS (e.g., HRQoL, symptoms, harms) that are important to patients, clinicians, and drug plans.

Economic Evidence

Cost and Cost-Effectiveness

Table 1: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-Utility Analysis Partitioned Survival Model (PSM)
Target population	Adult patients with KRAS G12C-mutated locally advanced (not amenable to curative therapy) or metastatic NSCLC who have received at least one prior systemic therapy.
Treatment	Sotorasib monotherapy
Dose regimen	960 mg once daily until disease progression or unacceptable toxicity.
Submitted price	$48.24 per 120 mg tablet
Treatment cost	28-Day Cost: $10,806

Component	Description
Comparator	Docetaxel monotherapy
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data sources	CodeBreaK 200 Trial
Key limitations	• Uncertainty in the overall survival (OS) benefit. In the CodeBreaK 200 trial the OS HR for sotorasib vs. docetaxel was 1.01 (95% CI, 0.77 to 1.33). As the trial allowed for crossover, the sponsor conducted a sensitivity analysis to adjust for this. Using the two-stage approach the adjusted HR for OS decreased to 0.823 (95% CI, 0.14 to 1.33). However, in the submitted analysis the sponsor used a HR with a much smaller CI of (95% CI, 0.69 to 0.98). This was considered less appropriate than using the CI from the two-stage method as it relied on external data rather than using data from the trial. Likewise, the method relied on an assumed relationship between PFS and OS which would have been more appropriate to explore using a Markov approach as a PSM assumes independence between PFS and OS. • Utilities were estimated using a time-to-death approach rather than for each health state. The methods for why certain time points before death were selected was unclear and this method assumes the only utility impact of progression is on time-to-death. Likewise, the disutilities related to AEs and drug administration were excluded. As sotorasib is an oral therapy and docetaxel is administered intravenously, excluding the disutility associated with IV administration underestimates the potential benefit associated with sotorasib. • Costs relevant to the health system were excluded in the sponsor's base case, including monitoring and nondrug disease management costs. • The cost-effectiveness of sotorasib compared with other therapies used in this setting, such as doublet platinum chemotherapy, is unknown. However, clinical experts consulted for this review noted it was unlikely sotorasib would displace doublet platinum chemotherapy given the lack of comparative evidence. • CADTH noted the probabilistic analysis resulted in erroneous results that were not clinically valid. Unnecessary calculations were also made for a partitioned survival model.
CADTH reanalysis results	• The CADTH base case addressed some of the key limitations from the sponsor's submission. The OS HR generated by the sponsor using the two-stage approach was used; utilities were determined by progression-status and incorporated impacts of AEs and IV administration; corrections were made to the calculation of state membership, and all relevant health care costs were included. • In the CADTH base case, the ICER for sotorasib relative to docetaxel is $308,262 per QALY gained. An 80% price reduction for sotorasib is required to obtain an ICER below a threshold of $50,000 per QALY gained.

AE = adverse events; CI = confidence interval' HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival mode; QALY = quality-adjusted life-year.

Budget Impact

The CADTH base case included 2 key revisions to the sponsor-submitted budget impact analysis. First, changes were made to the market share assumptions to reflect a faster uptake of sotorasib and a smaller market size, as it was assumed that sotorasib would only displace docetaxel. Second, changes were made to provincial coverage rates. The sponsor assumed a flat rate of public coverage of 80% across all drug plans. This estimate was replaced with estimates specific to the drug plans considered in the pan-Canadian analysis. In the CADTH base case, the expected budget impact of sotorasib in the Health Canada indicated

population from the drug plan perspective was estimated to be $9,351,339 in year 1, $11,248,227 in year 2, and $11,598,915 in year 3. The three-year net budget impact was estimated to be $32,198,481.

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation to not reimburse sotorasib for the treatment of adult patients with KRAS G12C-mutated locally advanced (not amenable to curative therapy) or metastatic NSCLC who have received at least 1 prior systemic therapy. In their request, the sponsor identified the following issues:

- The sponsor requested to change the recommendation category from Do Not Reimburse to a positive reimbursement category. The sponsor highlighted the unmet need in the target patient population given the lack of well-tolerated efficacious treatments and requested to align the CADTH recommendation with clinical practice guidelines that recommend sotorasib in the present target patient population.
- The sponsor requested pERC to redeliberate considering the clinician group input received from LCC and to incorporate a summary of this clinician group input into the recommendation document. The sponsor noted that the LCC clinician group emphasized the large unmet need for effective treatment options and strongly supported funding of sotorasib in the target patient population.
- The sponsor highlighted that PFS and ORR are clinically meaningful end points to patients with NSCLC. The sponsor requested that patient and clinician group, as well as clinical expert input regarding the clinical meaningfulness of PFS and ORR end points, be considered during the reconsideration meeting. The sponsor emphasized that, to assess PFS differences between study groups, the HR and Kaplan-Maier estimates across different time points should be considered in addition to median PFS.
- The sponsor requested pERC to reassess harms results in CodeBreaK 200 considering treatment-related and exposure adjusted AEs, and clinical experts' opinion that TEAEs observed with sotorasib could be adequately managed in clinical practice and appeared favourable compared with docetaxel. According to the sponsor the HRQoL results from the available evidence were supportive of patients receiving sotorasib experiencing symptom stabilization and improvement over time compared with docetaxel.
- The sponsor requested pERC to redeliberate considering equitable access to treatments for patients with NSCLC and KRAS G12C mutations in Canada and internationally.
- The sponsor requested the committee to redeliberate the totality of the evidence for sotorasib in light of results from CodeBreaK 200 supporting improvements in PFS, response outcomes, and tumour shrinkage in patients receiving sotorasib. The sponsor also requested the committee to redeliberate the OS evidence in the context of OS results from CodeBreaK100 and sensitivity analyses of OS that adjusted for the effect of crossover.

In the meeting to discuss the sponsor's request for reconsideration, the committee considered the following information:

- feedback on the draft recommendation from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- feedback from 2 clinical specialists with expertise diagnosing and treating patients with NSCLC
- feedback on the draft recommendation from 1 patient group: LCC
- feedback on the draft recommendation from 2 clinician groups: OH-CCO's LC DAC and LCC
- feedback on the draft recommendation from the public drug plans.

pERC Information

Members of the Committee at the Initial Meeting

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Initial meeting date: September 12, 2023

Regrets: 1 expert committee member did not attend

Conflicts of interest: None

Members of the Committee at the Reconsideration Meeting

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Reconsideration meeting date: February 14, 2024

Regrets: 3 expert committee members did not attend

Conflicts of interest: None

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