Canada's Drug Agency
L'Agence des médicaments du Canada

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Drugs Health Technologies Health Systems

Reimbursement Review

Regorafenib

Requester: Public drug programs
Therapeutic area: Osteosarcoma

Key Messages

What Is Metastatic Osteosarcoma?

- Bone tumours account for less than 1% of diagnosed cancers every year.
- Osteosarcoma is 1 of the most common primary bone tumours. Metastatic osteosarcoma is bone cancer that has spread to other parts of the body.
- Patients who present with metastatic disease at diagnosis or develop metastases during or after therapy have very poor outcomes with little chance of cure, with an average survival rate of less than 20% after 5 years.

What Are the Treatment Goals and Current Treatment Options for Metastatic Osteosarcoma?

- The goals of treatment for metastatic osteosarcoma are to improve symptoms, delay disease progression, and prolong life.
- Treatment typically includes cytotoxic chemotherapy in combination with surgery to remove the primary tumour.
- Patients with metastatic osteosarcoma whose disease progresses after initial chemotherapy have few treatment options other than other systemic treatments.

What Is Regorafenib and Why Did We Conduct This Review?

- Regorafenib is a type of targeted drug called a cancer growth blocker (receptor tyrosine kinase inhibitor) and is available as an oral tablet. Health Canada has approved regorafenib for colorectal, gastrointestinal, and liver cancers. For patients with osteosarcoma, regorafenib has been available through a manufacturer special access program that will shortly be ended.
- At the request of the participating public drug programs, we reviewed regorafenib to inform a recommendation on whether it should be reimbursed by public drug plans for patients with metastatic osteosarcoma who have had at least 1 prior systemic therapy.

How Did We Evaluate Regorafenib?

- We reviewed the clinical evidence on the beneficial and harmful effects of regorafenib and compared its costs versus other treatments used in Canada for patients with metastatic osteosarcoma. Ifosfamide with or without etoposide, cyclophosphamide and topotecan, and gemcitabine

Key Messages

with or without docetaxel were considered relevant treatments to compare with regorafenib.

- The clinical evidence was identified through systematic searches for available studies.
- The review was also informed by 1 patient group submission and 1 clinician group submission, in response to our call for input, and also from the participating public drug programs around issues that may impact their ability to implement a recommendation. We consulted 2 medical oncologists as part of the review process.

What Did We Find?

Clinical Evidence

- We reviewed 2 randomized controlled phase II trials (REGOBONE, SARC024) comparing regorafenib with placebo in patients with metastatic osteosarcoma who had received at least 1 line of systemic therapy.
- The results suggest a benefit of regorafenib for prolonging the time from treatment until disease worsening or death.
- There was no clear benefit of regorafenib in extending life.
- There were no reported data to assess the effect of regorafenib on quality of life.
- Regorafenib leads to a higher frequency of adverse events (AEs).
- Lack of data on the efficacy and safety of regorafenib in patients younger than 18 years and compared to other current treatment options are key evidence gaps.

Economic Evidence

- Reimbursing regorafenib for the treatment of adult and pediatric patients with metastatic osteosarcoma who have received, and whose disease has progressed on, at least 1 prior line of therapy is expected to increase costs to the public drug programs.

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Abbreviations

AE	adverse event
CDA-AMC	Canada’s Drug Agency
CI	confidence interval
ECOG	Eastern Cooperative Oncology Group
HRQoL	health-related quality of life
ITC	indirect treatment comparison
OS	overall survival
PFS	progression-free survival
TKI	tyrosine kinase inhibitor

Background

Introduction

The objective of the Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of regorafenib 160 mg tablets for oral administration in the treatment of patients with metastatic osteosarcoma who have received at least 1 prior line of therapy. The focus will be placed on comparing regorafenib to relevant comparators and identifying gaps in the current evidence. The economic review consists of a cost comparison for regorafenib compared with relevant comparators for the same population. The comparators considered relevant to the reviews were placebo and chemotherapeutic agents (ifosfamide with or without etoposide, cyclophosphamide and topotecan, and gemcitabine with or without docetaxel).

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug (product)	Regorafenib (Stivarga), 40 mg film-coated tablets for oral administration
Relevant Health Canada indication	Not applicable
Mechanism of action	Tyrosine kinase inhibitor
Recommended dosage	160 mg daily
Data protection status	Expired September 11, 2021
Patent status	4 patents, expiration dates from August 29, 2025, to April 8, 2031
Status of generic drugs/biosimilars	2 under review
Information on the CDA-AMC review	
Requester	Provincial Advisory Group
Indication under consideration for reimbursement	Metastatic osteosarcoma for patients who have received at least 1 prior line of therapy

CDA-AMC = Canada's Drug Agency.

Sources of Information

The contents of the Clinical Review report are informed by studies identified through systematic literature searches and input received from interested parties.

Calls for patient group, clinician group, and industry input are issued for each nonsponsored reimbursement review. Two patient group submissions were received — 1 from the Sarcoma Cancer Foundation of Canada and 1 from the Advocacy for Canadian Childhood Oncology Research Network (Ac2orn) — and 1 clinician group submission was received from the Pediatric Oncology Group of Ontario. Sarcoma Cancer Foundation of Canada gathered information by sharing an e-survey to a targeted group, followed by one-on-one discussions and interviews with interested participants. Ac2orn conducted short one-on-one interviews with families to collect first-hand experiences with regorafenib. The clinician group used a consultative process

to seek input from pediatric sarcoma experts in Ontario. The full submissions received are available on the project landing page in the consolidated input document.

Input from patient and clinician groups was considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical evidence. Relevant patient and clinician group input and industry input is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections.

The drug programs provide input on each drug being reviewed through the reimbursement review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized and provided to the expert committee in a separate document.

Each review team includes at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process. Two specialists with expertise in the diagnosis and management of osteosarcoma participated as part of the review team, with representation from Manitoba and Alberta.

Disease Background

Bone cancers are relatively rare, accounting for less than 1% of diagnosed cancers every year.[1] There are 3 kinds of primary bone cancers: osteosarcoma, Ewing sarcoma, and chondrosarcoma.[2] Osteosarcoma is the most common — it starts in new tissue in growing bones of children and adolescents, most often in the knee or upper arm areas. In older patients, it may arise in the axial skeleton, often complicating Paget disease. The age at incidence of osteosarcoma diagnosis is bimodal with a primary peak in adolescence and early adulthood (aged 15 to 20 years) and a second, smaller peak in the seventh and eighth decades of life; with incidence rates of approximately 8 and 6 cases per million person-years, respectively.[3] The peak in incidence at the time of adolescence and young adulthood is often attributed to the hormonal changes that occur during puberty.[4] In adults (older than 40 years) and older adults (older than 60 years), osteosarcoma tends to occur secondary to other conditions such as Paget disease of the bone, secondary to other benign bone conditions, or as a late effect of radiation therapy.[4] The key pathophysiological mechanism involves several possible genetic drivers of disease linked to bone formation, causing malignant progression and metastasis. The underlying symptoms of osteosarcoma are bone pain that varies depending on the size and location of the tumour in the bone, a swelling in the area of the tumour, a broken bone, and decreased mobility and problems moving the joint in the area. The diagnosis of osteosarcoma is made following the biopsy of a mass located most commonly at the metaphysis of the long bones. Approximately 80% of patients with osteosarcoma present with radiographically localized disease. Those patients with radiographically confirmed nonmetastatic osteosarcoma have a 5-year event-free survival of about 60%. In those who present with a primary lesion and an isolated pulmonary nodule, 5-year event-free survival is less than 20%.[5]

Current Management

Treatment Goals

In their input, the patient group noted that osteosarcoma is often a debilitating cancer with extreme pain, immobility, and other symptoms. The severe symptoms often cause patients to become unable to work and participate in day-to-day activities, unable to sleep, and ultimately unable to support themselves and maintain independence. Osteosarcoma is often associated with severe pain, and because it can develop anywhere in the body, surgical treatment can result in severe consequences, including limb loss and other long-term effects. The input from both patient groups highlighted the significant challenges faced by often young patients after getting a diagnosis of osteosarcoma and the importance of accessible treatments that prioritize quality of life for both patients and their families. The clinical experts also indicated that the main treatment goals in patients with metastatic osteosarcoma are to alleviate symptoms and improve quality of life, delay disease progression, and extend survival.

Current Treatment Options

Treatment of osteosarcoma typically includes cytotoxic neoadjuvant and adjuvant chemotherapy in combination with surgical resection of the primary tumour. According to the input provided by the clinician group, despite multiple clinical trials aimed at improving survival, the current standard of care usually used in the first-line setting remains MAP chemotherapy (methotrexate, doxorubicin, and cisplatin) — the same drug combination that has been used for the past 30 years. In the second line of treatment, ifosfamide and etoposide are commonly used. When these options are exhausted, third-line treatments and beyond may include other chemotherapy combinations such as docetaxel and gemcitabine. However, the response rates to these treatments are generally low and provide only temporary relief.

Key characteristics of regorafenib are summarized with other treatments available for metastatic osteosarcoma in the Supplemental Material document, in the Key Characteristics table in Appendix 1.

Unmet Needs and Existing Challenges

Although surgery combined with cytotoxic chemotherapy has significantly increased the chances of curing osteosarcoma, recurrent and refractory disease still poses a tough therapeutic challenge. The clinician group noted that although patients presenting with localized osteosarcoma have an expected overall survival (OS) approaching 80%, those who present with metastatic disease at diagnosis or who develop metastases during or after therapy have very poor outcomes with only a remote chance of cure, averaging less than 20% at 5 years. While metastasectomy can be a viable and potentially curative option for some patients, particularly those with limited pulmonary metastases and a long disease-free interval, most patients must rely on second-line systemic therapy. This therapy primarily aims to prolong life rather than cure the disease. Second-line therapies typically use a variety of cytotoxic agents, including ifosfamide and etoposide, gemcitabine and docetaxel, and cyclophosphamide and topotecan. Currently, there is no standardized treatment options for second-line chemotherapy or the use of investigational drugs. The clinician input noted that these regimens generally have modest efficacy and require multiple IV infusions, either in clinics or as inpatients with multiple and/or prolonged hospital visits. Furthermore, they carry significant risks of infection and the need for blood product support, requiring additional clinic visits and potentially hospitalizations,

and they have a significant negative impact on quality of life due to hair loss, nausea and vomiting, fatigue, immunosuppression, and the need for intensive supportive care associated with cytotoxic chemotherapy. The patient groups noted the challenges of further chemotherapy and hospitalizations and indicated that regorafenib treatment enabled patients to spend more time outside the hospital with their families. One caregiver interviewed by Ac2orn said that, although it was unclear if regorafenib extended her 15-year-old daughter's life, it gave her the opportunity to pursue dreams and moments that mattered most to her.

The clinician group noted that regorafenib has several benefits that help address the large unmet need for effective and well-tolerated therapies for relapsed or progressive advanced osteosarcoma. According to clinician input, regorafenib is an oral agent with documented benefit at delaying progression that requires no planned hospital visits or admissions and that carries little to no risk of infection or need for blood transfusions related to cytopenias. Importantly, it enhances the quality of life for patients with an otherwise poor prognosis through improved disease control, minimization of AEs from therapy, and convenient oral administration. Regorafenib is expected to represent a treatment option that is better tolerated than available second-line therapies, associated with improved compliance (especially in adolescents), and far more convenient than IV therapy administered in hospital.

The clinical experts consulted by Canada's Drug Agency (CDA-AMC) noted that most jurisdictions in Canada only have access to cytotoxic chemotherapy as first or later lines of therapy (cisplatin, doxorubicin, methotrexate, gemcitabine, docetaxel, ifosfamide, etoposide). Targeted therapies, especially tyrosine kinase inhibitors (TKIs), are not available. TKIs like regorafenib have a unique mechanism of action that fills an unmet need with the added advantage of being an oral drug with easy administration. Furthermore, regorafenib can be used in patients who cannot tolerate the side effects of cytotoxic chemotherapy, particularly myelosuppression.

Considerations for Using the Drug Under Review

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review and from clinician groups. The following has been summarized by the review team.

Place in Therapy

The clinical experts consulted indicated that all patients should have previously failed or shown intolerance to treatment with doxorubicin and cisplatin. Regorafenib targets angiogenesis, which is not a mechanism targeted by standard chemotherapy drugs. No drugs targeting angiogenesis are currently approved for osteosarcoma in Canada. The clinical experts noted that regorafenib after first-line chemotherapy would not be a shift in the current treatment paradigm but represents a good option to preserve patient quality of life as compared to further treatment with cytotoxic agents. Regorafenib would not replace any existing second-line options but would be considered as additional therapy after first-line chemotherapy. For most patients, this treatment can be considered as palliative treatment. Regorafenib would be best used as second-line therapy after chemotherapy. Most patients would not get a chance to try more treatments because of the progression of the disease and rapid decline of functional status, so it is best used after first-line systemic treatment.

The clinician group indicated that clinicians treating patients with osteosarcoma should consider regorafenib as a first-line therapy option following first relapse or progression. They further noted that regorafenib can be offered as maintenance therapy for high-risk patients completing first-line upfront therapy who are not eligible for clinical trials evaluating maintenance therapy in osteosarcoma.

Patient Population

The clinical experts indicated that any patient with conventional osteosarcoma aged 10 years or older should be eligible for treatment with regorafenib if they are intolerant to cisplatin and doxorubicin alone or in combination or when this treatment was not effective. Regorafenib is only given when patients have stage IV disease and only in cases of significant disease progression, regardless of symptoms, because these patients deteriorate quite rapidly if rapid radiographic disease progression is not treated quickly.

The clinician group indicated that patients with unresectable metastatic osteosarcoma (upfront or at relapse) would be eligible and most likely to benefit from therapy with regorafenib. Because these young patients are otherwise going to die from their disease, they all deserve some form of therapy to help prolong their lives and ensure good quality of life. Patients would be identified through routine oncology clinic visits, with baseline investigations including bloodwork and chest imaging (chest X-ray and CT scan).

Assessing the Response to Treatment

The clinical experts noted that there is no biomarker to predict response, but slower-growing tumours may respond to TKIs better than faster-growing tumours. Symptom improvement would be considered a sign that the patient is responding to treatment. CT of affected organs every 2 to 3 months is reasonable to assess radiologic response.

The clinician group indicated that outcome measures used in clinical trials mirror those employed in clinical practice, including serial CT scan surveillance of lung metastases (i.e., every 12 weeks). The lack of progression on imaging (i.e., assessed using the Response Evaluation Criteria in Solid Tumours [RECIST]) and patient-reported symptoms (i.e., pain, respiratory distress, hemoptysis) would warrant ongoing therapy. This criterion is standard and consistent across hospitals and oncology physicians.

Discontinuing Treatment

The clinical experts stated that obvious disease progression not amenable to local therapies like surgery or radiation, and intolerable side effects like hand-foot syndrome and mucositis, would be reasons to discontinue treatment with regorafenib.

The clinician group also indicated that disease progression and intolerance can lead to discontinuation of regorafenib treatment. They further noted that there is an opportunity for dose modification in the setting of toxicity that exceeds grade 3/4 without any documented impact on efficacy. Most patients who develop toxicity can continue treatment with a modification of their dose.

Prescribing Considerations

Both the clinical experts and the clinician group indicated that regorafenib should only be initiated under the direction of an oncology team with experience in caring for osteosarcoma and managing adverse side

effects. The drug is orally administered at home, and AEs, including laboratory monitoring, can often be managed with community labs and resources.

Clinical Review

Methods

We conducted a systematic review to identify evidence for regorafenib for the treatment of patients with metastatic osteosarcoma. Studies were selected according to the eligibility criteria in Table 2. We also searched for long-term extension studies of included randomized controlled trials, indirect treatment comparisons (ITCs) that adhered to the eligibility criteria (except for the study design criteria), and studies addressing gaps that did not meet the eligibility criteria but were considered to address important gaps in the systematic review evidence.

Relevant comparators included treatments used in clinical practice in Canada in the patient population under review. We selected outcomes (and follow-up times) for review considering clinical expert input and patient and clinician group inputs. Selected outcomes are those considered relevant to expert committee deliberations. Detailed methods for literature searches, study selection, and data extraction are in the Supplemental Material in Appendix 2.

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Patients (adult and pediatric) with metastatic osteosarcoma who have received and progressed on at least 1 prior line of therapy
Intervention	Regorafenib (160 mg orally on days 1 to 21 of each 28-day cycle)

Comparator	• Placebo
	• Other chemotherapeutic agents:
	  ◦ ifosfamide with or without etoposide
	  ◦ cyclophosphamide and topotecan
	  ◦ gemcitabine with or without docetaxel

Outcomes	**Efficacy outcomes:** • Progression-free survival • Overall survival • Response on serial imaging • HRQoL (and overall symptoms improvement) **Harms outcomes:** AEs, SAEs, discontinuation due to AEs, mortality
Study design	Published and unpublished phase III and IV RCTs If no phase III or IV studies are identified, phase II studies or prospective observational studies may be considered.

AE = adverse event; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event.

Clinical Evidence

From the search for primary studies, we identified 314 unique records via the searches of databases and registers, of which we excluded 312 by title and abstract. We screened 2 records by full text and included 2 reports of 2 studies.

From the search for ITCs, we identified 579 unique records via the searches of databases and registers, of which we excluded 579 by title and abstract. No potentially relevant ITCs were identified.

Systematic Review

Description of Studies

Detailed characteristics of the included studies (REGOBONE and SARC04) are summarized in Table 3.

REGOBONE

REGOBONE is a phase II, double-blind, randomized placebo-controlled trial designed to assess the efficacy and safety of regorafenib for patients with progressive metastatic osteosarcoma and other bone sarcomas.[6] The trial comprised 4 parallel independent cohorts of different histological subtypes of metastatic bone cancers (osteosarcoma, Ewing sarcoma, chondrosarcoma, and chordoma). The trial took place between October 10, 2014, and April 4, 2017, and included 43 adult patients with histologically confirmed osteosarcoma whose disease had progressed after treatment with 1 to 2 previous lines of chemotherapy for metastatic disease that was not amenable to treatment with curative intent. These patients were enrolled from 13 French comprehensive cancer centres and were randomly assigned (2:1) to receive either oral regorafenib 160 mg per day (four 40 mg oral tablets for 21 of 28 days) or matching placebo tablets. Patients in both groups also received best supportive care, which included any method to preserve the comfort and dignity of the patients and excluded any disease-targeting antineoplastic agent, such as any kinase inhibitor, chemotherapy, radiotherapy, or surgical intervention. The study protocol was amended to allow inclusion of patients aged 10 years and older; however, only adult patients could be recruited.

Serial tumour size assessment by CT imaging was done every 4 weeks for the first 4 months and then every 8 weeks (every second cycle) until the end of study treatment. For patients in the placebo group who crossed over to receive open-label regorafenib after centrally confirmed disease progression and unblinding, disease restaging was resumed at the original schedule (i.e., every 4 weeks for the first 4 months, and then every 8 weeks [every second cycle]) until the end of study drug treatment. All patients entered the follow-up period 30 days after discontinuation of study treatment.

The primary end point was the proportion of patients without disease progression at 8 weeks. Secondary end points included progression-free survival (PFS) (assessed centrally according to modified RECIST version 1.1), objective responses (the proportion of patients who achieved a complete or partial response as their best response since randomization, according to modified RECIST version 1.1), and OS (defined as the time from randomization until the date of death from any cause).

SARC024

SARC024 is a phase II, double-blind, randomized placebo-controlled trial of regorafenib in patients with metastatic osteosarcoma, carried out across 12 centres in the US.[7] Eligible patients were aged 10 years and older with a diagnosis of advanced or metastatic bone or extraskeletal osteosarcoma and at least 1 prior line of systemic therapy in the neoadjuvant, adjuvant, or metastatic setting, and measurable disease by RECIST version 1.1, with evidence of progressive disease within 6 months of enrolment. Patients received either placebo or regorafenib at an initial dose of 160 mg (four 40 mg oral tablets for 21 of 28 days). Patients continued to receive study treatment until either RECIST (version 1.1) progression, more than 28 days had elapsed since the last dose of the study drug, or patient- or physician-initiated discontinuation.

Tumour assessments were performed by the investigators using RECIST version 1.1. A baseline study scan was required within 28 days of cycle 1 of day 1. Thereafter, tumour assessments were performed every 8 weeks for the first 32 weeks and then every 12 weeks, with a 6- to 7-day window of the anticipated scan date.

The primary end point was median PFS. Secondary end points included incidence of AEs (according to Common Terminology Criteria for Adverse Events version 4.03), overall response rate per RECIST (version 1.1), time to tumour progression, PFS at 8 and 16 weeks, and OS. Additional secondary end points included PFS, OS, overall response rate, and time to tumour progression after crossover.

Table 3: Characteristics of Included Studies

Study name, design, sample size	Key eligibility criteria	Intervention and comparator	End points
Duffault, et al. (2019) **REGOBONE** Phase II, multicentre, double-blind, placebo-controlled trial N = 43	• Aged 10 years or older • Adequate performance status (adults: ECOG performance status of 0 to 1; children aged > 12 years with a score of ≥ 60% on the Karnofsky performance scale; children aged ≤ 12 years with a score of ≥ 60% on the Lansky scale) • Histological diagnosis of osteosarcoma • Objective disease progression within 3 months before study entry per RECIST version 1.1 • Disease not amenable to treatment with curative intent • Previously treated with 1 to 2 lines of chemotherapy for metastatic disease, with at least 4 weeks since the last chemotherapy (6 weeks in the case of nitrosoureas and mitomycin C), immunotherapy, or any other pharmacological treatment and/or radiotherapy • A body surface area of at least 1.30 m^2 • Life expectancy of longer than 3 months	*Intervention:* best supportive care + regorafenib 160 mg orally per day (4 tablets of 40 mg once daily) *Comparator:* best supportive care + matching placebo tablets	*Primary end point:* Proportion of patients without disease progression at 8 weeks *Secondary end points:* • PFS • Objective response • Overall survival • Safety and tolerability

Study name, design, sample size	Key eligibility criteria	Intervention and comparator	End points
	• Adequate bone marrow function (absolute neutrophil count ≥ 1 + 5 × 10^9 cells/L, platelets ≥ 100 × 10^9/L, hemoglobin concentration ≥ 9 g/dL), normal renal function (serum creatinine ≤ 1 + 5 × ULN, glomerular filtration rate ≥ 30 mL/min per 1.73 m^2 according to the modified diet in renal disease abbreviated formula, and normal spot urine analysis), normal liver function (aspartate aminotransferase and alanine aminotransferase ≤ 2 + 5 × ULN [or ≤ 5 + 0 × ULN for patients with liver involvement of their cancer], bilirubin ≤ 1 + 5 × ULN, and alkaline phosphatase ≤ 2 + 5 × ULN [or ≤ 5 × ULN in those with liver involvement of their cancer]), and normal pancreatic function (lipase ≤ 1 + 5 × ULN)		
Davis, et al. (2019) **SARC024** Phase II, multicentre, double-blind, placebo-controlled trial N = 42	• Aged 10 years or older • Advanced or metastatic bone or extraskeletal osteosarcoma • Body surface area of 0.65 m^2 or greater • WHO performance status of 0 to 2 (with prespecified maximum of 16 patients with WHO performance status of 2) • At least 1 prior line of systemic therapy in the neoadjuvant, adjuvant, or metastatic setting • Adequate organ function • Ability to swallow oral medication • Measurable disease by RECIST (version 1.1), with evidence of progressive disease within 6 months of enrolment	*Intervention:* regorafenib 160 mg orally per day (4 tablets of 40 mg once daily) *Comparator:* placebo	*Primary end point:* PFS (median) *Secondary end points:* • Incidence of AEs • Overall response rate per RECIST (version 1.1) • Time to tumour progression • PFS (at 8 and 16 weeks) • OS • PFS, OS, overall response rate, and time to tumour progression after crossover

AE = adverse event; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; PFS = progression-free survival; ULN = upper limit of normal.
Source: Duffaud et al. (2019),[6] Davis et al. (2019).[7]

Statistical Testing and Analysis Populations

REGOBONE

Sample size was calculated by the A'Hern single-stage design for phase II trials.[8] The number of patients to include was calculated based on an assumed median PFS of 6 weeks without active treatment and 12 weeks with treatment. No comparative hypothesis was formulated, and no statistical comparison between the control and experimental group was planned. The placebo group was only included to check the similarity between the enrolled patients and historical controls with respect to clinical outcome when given standard treatments. Thereby, the primary end point and all other efficacy outcomes were analyzed among

the modified intention-to-treat population, including all patients who initiated study drug treatment, with no major protocol violations.

The percentages of patients who were progression-free at 8 weeks in each group were calculated with their respective 95% confidence intervals (CIs) (which were 1-sided due to the Fleming design). PFS and OS were estimated using the Kaplan-Meier method and were summarized as medians or time point–specific probabilities in each arm, along with the corresponding 2-sided 95% CIs. For patients who were event-free at the time of the analysis, PFS was censored at the date of the final adequate tumour assessment. OS was censored at the date of last contact for patients who were still alive.

SARC024

A sample size consisting of 42 events was needed to detect a between-group difference of 3 months in median PFS. The design aimed to achieve 90% power at a 5% 1-sided type I error, with an expectation that 48 patients would be sufficient to observe the target number of events. After the release of the REGOBONE trial results, an independent data safety and monitoring board recommended closing the study after the enrolment of 42 of 48 planned participants and observing 31 of the intended 42 PFS events.

All analyses were conducted in the intention-to-treat population. Patients were stratified by WHO performance status (0 to 1 versus 2) and by number of prior lines of therapy (1 versus 2 or more). OS and PFS were estimated using a Kaplan-Meier estimator, and between-group differences were tested using a 1-sided stratified log-rank test. Reported P values were not adjusted for multiple comparisons.

Patient Disposition

REGOBONE

Between October 10, 2014, and April 4, 2017, 43 adult patients were enrolled from 13 French comprehensive cancer centres and randomly assigned 2:1 to receive regorafenib or placebo. Five patients (2 in the placebo group and 3 in the regorafenib group) had major protocol violations and were not included in the full analysis set (no documented progressive disease at inclusion n = 4, no measurable lesions at inclusion n = 1). Two patients who were initially enrolled in the REGOBONE chondrosarcoma cohort had their diagnoses changed to osteosarcoma after central histological review (1 of whom was randomly assigned to regorafenib and the other to placebo); data from both these patients were incorporated into the osteosarcoma cohort. In total, 38 adult patients with histologically confirmed advanced osteosarcoma constituted the population for the efficacy analysis: 26 patients were randomly assigned to regorafenib and 12 to placebo. Twelve patients discontinued placebo (10 progressions, 1 withdrawal, 1 progression not confirmed). Ten out of 12 patients originally assigned to placebo crossed over to open-label regorafenib. All 12 patients died (11 progressive disease, 1 toxicity -alteration of general state due to cancer). Of the 26 patients initially assigned to regorafenib all 26 stopped the study (21 deaths due to progressive disease, 5 alive at database lock). No patient remained on treatment at the time of the reported analysis

SARC024

A total of 42 patients were recruited from 12 centres across the US between September 2014 and May 2018; 22 patients were randomly assigned to regorafenib, and 20 patients were randomly assigned to placebo. In the regorafenib arm, 11 patients discontinued treatment due to progressive disease, 3 withdrew consent, 2 discontinued due to intercurrent disease, and 5 discontinued for other reasons. In the placebo arm, 17 patients discontinued treatment due to progressive disease, 1 withdrew consent, and 2 discontinued treatment for other reasons. Ten patients initially assigned to placebo crossed over to the regorafenib arm upon progression. There were 12 deaths (54%) in the regorafenib arm and 10 (50%) in the placebo arm.

Baseline Characteristics

REGOBONE

The median age of the patients at baseline was 33 years (interquartile range: 22 to 50). Baseline characteristics were generally balanced except for age, sex, and Eastern Cooperative Oncology Group (ECOG) performance status. Median age was 32 years in the regorafenib arm and 40 years in the placebo arm. In the regorafenib arm, 73% of patients were male, compared to 42% in the placebo arm. In the regorafenib arm, 46% had an ECOG performance status of 1 versus 17% in the placebo arm. Most patients (79%) had only 1 previous chemotherapy regimen for metastatic disease at inclusion. Distant metastases were mainly in the lung and bone. Most patients had received the 3 most common drugs used for treating adults with osteosarcoma: doxorubicin, cisplatin, and ifosfamide. High-dose methotrexate had also been used in 10 (23%) of 43 patients overall. At the time of the analysis, the median follow-up of patients who were alive was 31.6 months (interquartile range: 24.1 to 33.6) (Table 4).

SARC024

The median age was 37 years (range: 18 to 76 years). The majority of patients (78.5%) had osteosarcoma. Baseline characteristics were generally balanced between the arms but were imbalanced in age and sex. Patients in the regorafenib arm were younger (median age: 33 compared to 47 in the placebo arm), and a lower proportion were male (6% versus 14% in the placebo arm) (Table 5).

Table 4: Baseline Characteristics — REGOBONE

Characteristic	Regorafenib group (n = 26)	Placebo group (n = 12)	Excluded from efficacy analysis (n = 5)
Age, years, median (IQR)	32 (21 to 50)	40 (29 to 43)	30 (23 to 43)
Sex			
Male	19 (73%)	5 (42%)	4 (80%)
Female	7 (27%)	7 (58%)	1 (20%)
ECOG performance status			
0	12 (46%)	2 (17%)	2 (40%)
1	14 (54%)	10 (83%)	2 (40%)

Characteristic	Regorafenib group (n = 26)	Placebo group (n = 12)	Excluded from efficacy analysis (n = 5)
Unknown	0	0	1 (10%)
Presence of metastases			
No (locally advanced disease)	1 (4%)	0	2 (40%)
Yes	25 (96%)	12 (100%)	3 (60%)
Sites of metastases			
Lung	24 (92%)	10 (83%)	2 (40%)
Bone	6 (23%)	3 (25%)	0
Lymph node	3 (12%)	4 (33%)	0
Pleural	3 (12%)	1 (8%)	0
Previous lines of chemotherapy for metastatic disease			
1	21 (80%)	10 (83%)	3 (60%)
2	5 (20%)	2 (17%)	2 (40%)
0	0	0	0
Previous treatment at entry			
Doxorubicin	26 (100%)	12 (100%)	2 (40%)
Ifosfamide	24 (92%)	12 (100%)	3 (60%)
Cisplatin	25 (96%)	11 (92%)	1 (20%)
High-dose methotrexate	7 (27%)	3 (25%)	0
Etoposide	21 (81%)	5 (42%)	1 (20%)
Gemcitabine or docetaxel	3 (12%)	2 (16%)	0
Oral cyclophosphamide	3 (12%)	1 (8%)	2 (40%)

ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range.

Source: Duffaud et al. (2019).[6]

Table 5: Baseline Characteristics — SARC024

Characteristic	All patients (N = 42)	Regorafenib (n = 22)	Placebo (n = 20)
Age, years			
Median	37	33	47
Range	18 to 76	18 to 70	19 to 76
Sex, n			
Male	20	6	14
Female	22	16	6
Previous lines of therapy			

Characteristic	All patients (N = 42)	Regorafenib (n = 22)	Placebo (n = 20)
1	21 (50)	11 (50)	10 (50)
> 1	21 (50)	11 (50)	10 (50)
WHO performance status			
0 to 1	41 (98)	22 (100)	19 (95)
2	1 (2)	0 (0)	1 (5)
Primary tumour location			
Extremity	27 (64)	13 (59.1)	14 (70)
Head/neck	7 (17)	3 (13.6)	4 (20)
Pelvis/spine	4 (9.5)	3 (13.6)	1 (5)
Other	4 (9.5)	3 (14.6)	1 (5)
Histology			
Conventional osteosarcoma	33 (78.5)	17(77.2)	16 (80)
Conventional chondroblastic	15 (36)	7 (31.8)	8 (40)
Conventional NOS	9 (21)	5 (22.7)	4 (20)
Conventional osteoblastic	5 (12)	3 (13.6)	2 (10)
Conventional osteoblastic and chondroblastic	3 (7)	1 (4.6)	2 (10)
Conventional fibroblastic	1 (2)	1 (4.6)	0 (0)
Other osteosarcoma[a]	4 (9.5)	1 (4.6)	3 (15)
Osteosarcoma NOS	5 (12)	4 (18.2)	1 (5)

NOS = not otherwise specified.

[a]Other osteosarcoma includes juxtacortical, parosteal, and telangiectatic.

Source: Davis et al. (2019).[7]

Critical Appraisal

Internal Validity

In both the REGOBONE and SARC024 trials, randomization procedures were appropriate for limiting the risk of bias in the randomization process. However, due to the small sample sizes (n = 43 and n = 42), there were noticeable differences in prognostic variables, particularly in patients' demographic characteristics (age and sex in both trials and ECOG performance status in REGOBONE). Due to the observed imbalances, it is possible that the reported effects are overestimated or underestimated and may be an inaccurate estimate of the average treatment effects.

Both trials were phase II signal-seeking trials. REGOBONE was designed as a noncomparative trial and did not calculate P values. Both trials were double-blind with patients, caregivers, and trial personnel unaware of treatment assignments, which minimizes the potential for bias due to deviations from intended interventions. The key efficacy outcomes were objective (disease progression, PFS, objective response), so risk of bias in their measurement is unlikely. Both trials followed prespecified analysis plans with limited

evidence of selective reporting of prespecified outcomes. However, the REGOBONE trial lacked prespecified statistical between-group testing, which limits the interpretation of the significance of the reported effect estimates. SARC024 may be underpowered because the study stopped recruiting after the enrolment of 42 of 48 planned participants and 31 of the required 42 PFS events. This was done after the release of the REGOBONE trial results that showed a benefit of regorafenib compared to placebo and concerns regarding continuing enrolment in a placebo-controlled study. Both studies used the Kaplan-Meier method for time-to-event outcomes (PFS and OS). In both trials, patients crossed over from the placebo arm to the regorafenib arm; the crossover design compromises the ability to assess the long-term efficacy of regorafenib on OS.

External Validity

Both trials included patients with a confirmed diagnosis of metastatic osteosarcoma who had received at least 1 prior line of systemic therapy. Although both trials allowed the inclusion of patients aged 10 and older, only adult patients could be recruited. The clinical experts consulted by CDA-AMC indicated that both trial populations were reflective of clinical practice in Canada and further noted that, although the trials did not include pediatric patients, they considered that patients aged 10 and older with metastatic osteosarcoma may be considered for regorafenib treatment. The intervention (regorafenib dose), including the supportive care used in the REGOBONE trial, mirrors clinical practice. Prior regimens received before enrolment in the trials were also largely representative of clinical practice in Canada. Both trials compared regorafenib to placebo, which was a relevant comparator in this noncurative setting. Most outcomes considered important to the review were reported in the included studies; however, evidence for health-related quality of life (HRQoL) was not measured in either trial. As such, the effect of regorafenib compared to placebo on HRQoL in patients with metastatic osteosarcoma remains unknown.

Results

Efficacy

Results for outcomes important to this review are presented in the following sections.

Progression-Free Survival

REGOBONE

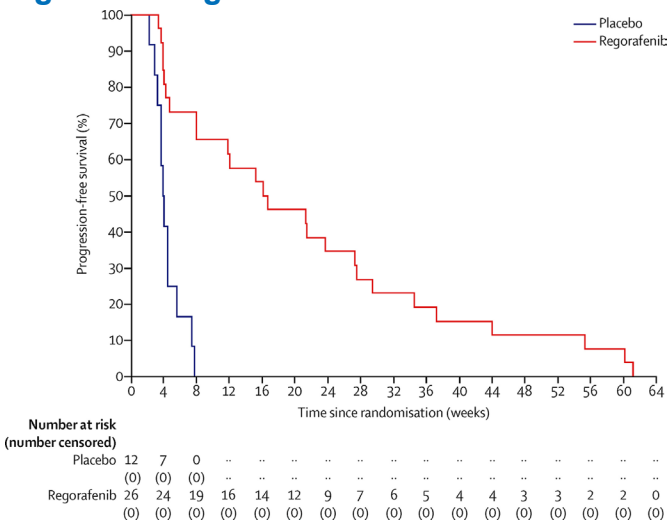
At the time of analysis (after data cut-off on April 18, 2018), disease had progressed in all 26 patients in the regorafenib group and all 12 patients in the placebo group, and 33 of 38 patients (87%) had died (21 of 26 patients [81%] in the regorafenib group versus all 12 [100%] in the placebo group). All but 1 death was due to disease progression.

Median PFS was 16.4 weeks (95% CI, 8.0 to 27.3) in the regorafenib group and 4.1 weeks (95% CI, 3.0 to 5.7) in the placebo group (Table 6, Figure 1).

Median PFS in the patients who crossed over to regorafenib was 19.4 weeks (95% CI, 3.6 to 27.7), but it is not comparable to other values because treatment crossover was conditional on progression during placebo.

PFS was 62% at 12 weeks and 35% at 24 weeks in the regorafenib group. No patients were progression-free at 12 weeks in the placebo group.

Figure 1: Progression-Free Survival — REGOBONE



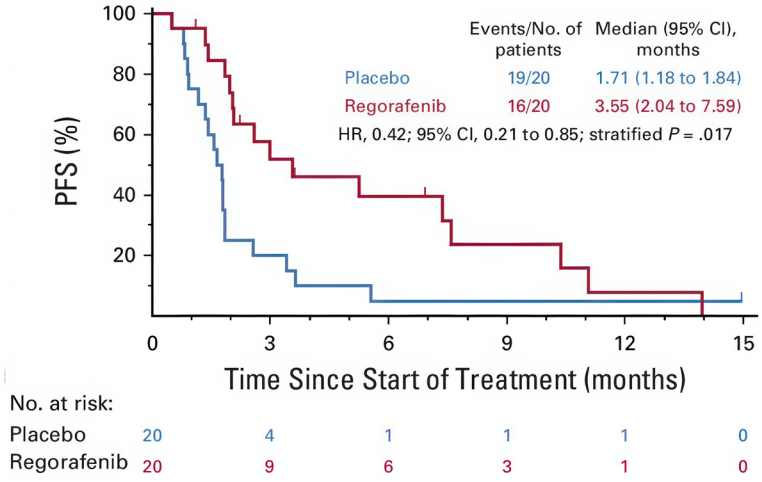
Source: Duffaud et al. (2019).[6] Reprinted from *The Lancet Oncol*, 20, Duffaud F, et al., Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study, 120-133, Copyright (2019), with permission from Elsevier.

SARC024

Median PFS was 3.6 months (95% CI, 2.0 to 7.6 months) for regorafenib and 1.7 months (95% CI, 1.2 to 1.8 months) for placebo (hazard ratio = 0.42; 95% CI, 0.21 to 0.85; P = 0.017) (Figure 2).

PFS at 8 weeks and 16 weeks was 79.0% and 44.4% for patients receiving regorafenib, respectively, compared with 25.0% (Fisher's exact test P = 0.001) and 10.0% (Fisher's exact test P = 0.027) for those who received placebo.

Figure 2: Progression-Free Survival — SARC024



CI = confidence interval; HR = hazard ratio; PFS = progression-free survival.

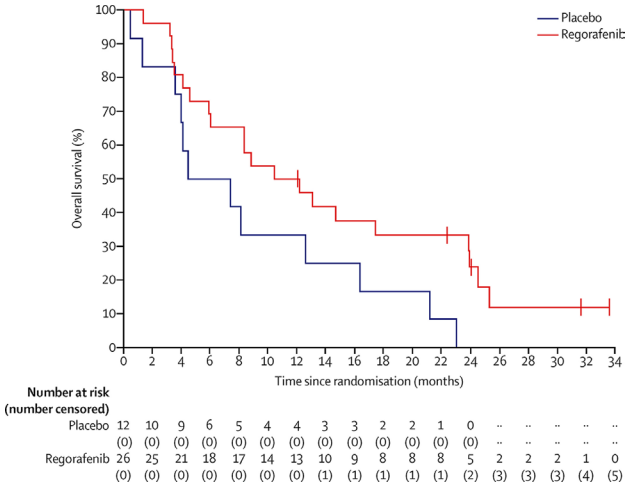
Source: Davis et al. (2019).[7] Reproduced with permission from Davis L. E. et al. Randomized Double-Blind Phase II Study of Regorafenib in Patients With Metastatic Osteosarcoma, *J Clin Oncol*, 37, 1424-1431. https://ascopubs.org/doi/10.1200/JCO.18.02374

Overall Survival

REGOBONE

Median OS was 11.3 months (95% CI, 5.9 to 23.9) in patients who received regorafenib and 5.9 months (95% CI, 1.3 to 16.4) in the placebo group (Figure 3).

Figure 3: Overall Survival — REGOBONE

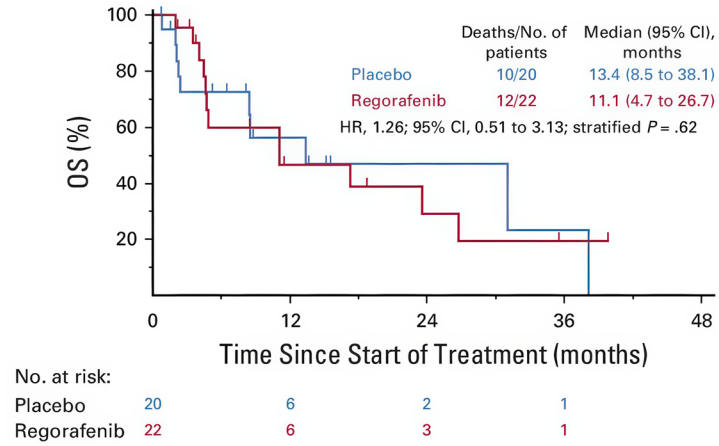


Source: Duffaud et al. (2019).[6] Reprinted from *The Lancet Oncol*, 20, Duffaud F, et al., Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study, 120-133, Copyright (2019), with permission from Elsevier.

SARC024

Median OS was 11.1 months (95% CI, 4.7 to 26.7 months) for patients initially randomly assigned to regorafenib and 13.4 months (95% CI, 8.5 to 38.1 months) for patients initially randomly assigned to placebo (hazard ratio = 1.26; 95% CI, 0.51 to 3.13; P = 0.62) (Figure 4).

Figure 4: Overall Survival — SARC024



CI = confidence interval; HR = hazard ratio; OS = overall survival.

Source: Davis et al. (2019).[7] Reproduced with permission from Davis L. E. et al. Randomized Double-Blind Phase II Study of Regorafenib in Patients With Metastatic Osteosarcoma, *J Clin Oncol*, 37, 1424-1431. https://ascopubs.org/doi/10.1200/JCO.18.02374

Table 6: Efficacy Outcomes — REGOBONE

Outcome	Regorafenib group (n = 26)	Placebo group (n = 12)
Nonprogressive disease at 8 weeks	17 (65%) (95% CI, 47–)[a]	0
Response at 8 weeks		
Complete response	0	0
Partial response	2 (8%)	0
Stable disease	15 (58%)	0
Progressive disease	9 (35%)	12 (100%)
Median PFS, weeks	16.4 (95% CI, 8.0 to 27.3)	4.1 (95% CI, 3.0 to 5.7)
PFS at 12 weeks	62% (95% CI, 40 to 77)	0
PFS at 24 weeks	35% (95% CI, 17 to 52)	0

CI = confidence interval; PFS = progression-free survival.

[a]One-sided 95% CI (due to the Fleming design).

Source: Duffaud et al. (2019).[6]

Response

REGOBONE

At 8 weeks, 8% of patients had a partial response, 58% had stable disease, and 35% had progressive disease in the regorafenib group. All patients randomized to receive placebo had progressive disease (Table 6).

SARC024

Three patients (13.6%) randomly assigned to regorafenib achieved partial response per RECIST (version 1.1). These patients had received 1, 3, and 5 lines of prior therapy, respectively. There were no objective responses in the placebo group.

Health-Related Quality of Life

HRQoL was not an end point in either trial.

Harms

REGOBONE

- In the safety population, 13 treatment-related serious AEs occurred in 7 of 29 patients (24%) in the regorafenib group versus none of 14 patients in the placebo group. All these treatment-related serious AEs in the regorafenib group were at least grade 3 severity and were hypertension (n = 3), hypophosphatemia (grade 4, n = 1; grade 3, n = 2), hand-foot skin reaction (n = 2), transaminases increase (n = 1), lipase increase (n = 1), blood alkaline phosphatase increase (n = 1), epilepsy (n = 1), and hemothorax (n = 1).

- The most common grade 3 or worse treatment-related AEs during the double-blind period in the regorafenib group included hypertension (7 of 29 patients [24%]), hand-foot skin reaction (3 of 29 patients [10%]), fatigue (3 of 29 patients [10%]), hypophosphatemia (3 of 29 patients [10%]), and chest pain (in 3 of 29 patients [10%]).
- There were no treatment-related deaths reported in either treatment group.

SARC024

- AEs were more frequent in the regorafenib arm than in the placebo arm; 91% of patients in the regorafenib arm had at least 1 AE of any grade compared to 60% of patients in the placebo arm.
- Patients treated with regorafenib experienced hand-foot skin reactions (grade 1 to 2 in 7 patients [32%] and grade 3 in 1 patient [5%] compared with no patients who received placebo) and gastrointestinal disorders (grade 1 to 2 in 11 patients [50%] compared with grade 1 to 3 in 5 patients [25%] who received placebo).
- Grade 3 hypertension occurred in 3 patients (14%) assigned to regorafenib, and an additional 4 patients (18%) experienced grade 2 hypertension; 3 patients (15%) who received placebo experienced grade 1 to 2 hypertension.

Table 7: Harms — SARC024

	Regorafenib (n = 22)		Placebo (n = 20)	
AE, n (%)	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any	20 (91%)	14 (64%)	12 (60%)	9 (45%)
Hand-foot skin reaction	8 (36%)	1 (5%)	0	0
Hypertension	7 (32%)	3 (14%)	3 (15%)	0
Nausea	5 (23%)	0	4 (20%)	1 (5%)
Diarrhea	4 (18%)	1 (5)	0	0
Oral mucositis	3 (14%)	0	0	0
Maculopapular rash	3 (14%)	2 (9%)	0	0
Vomiting	3 (14%)	0	1 (5%)	1 (5%)
Thrombocytopenia	2 (9%)	2 (9%)	0	0
Hypophosphatemia	2 (9%)	2 (9%)	1 (5%)	1 (5%)
Extremity pain	2 (9%)	2 (9%)	0	0

AE = adverse event.

Source: Davis et al. (2019).[7]

Discussion

Efficacy

Data from 2 similarly designed multicentre, randomized, phase II clinical trials comparing regorafenib to placebo in patients with metastatic osteosarcoma who have received at least 1 line of prior systemic therapy suggest a benefit of regorafenib in improving PFS. In the REGOBONE trial, which recruited patients out of

France, patients had an improved median PFS of 16.4 weeks (95% CI, 8.0 to 27.3) in the regorafenib arm compared to 4.1 weeks (95% CI, 3.0 to 5.7) in the placebo arm. However, this study did not include formal statistical between-group comparisons. Similarly, the SARC024 trial, which recruited patients out of the US, showed a median PFS of 3.6 (95% CI, 2.0 to 7.6) months for patients treated with regorafenib, versus 1.7 (95% CI, 1.2 to 1.8) months for the placebo arm (hazard ratio = 0.42; 95% CI, 0.21 to 0.85, P = 0.017). No significant differences were observed in OS. Of note, the crossover design in both trials compromises the ability to assess the effect of regorafenib compared to placebo on long-term OS. In both trials, partial tumour responses to regorafenib were observed in 7.6% and 13.6% of the regorafenib-treated patients in the REGOBONE and SARC024 trial, respectively. The differences in the observed PFS and OS across trials are indicative of a large heterogeneity in the patient population and introduce uncertainty surrounding the magnitude of effect of regorafenib on treating metastatic osteosarcoma in the Canadian context.

The clinical experts and clinician group indicated that, as with all treatments in the setting of metastatic disease, treatment goals for patients with metastatic osteosarcoma are to improve symptoms, delay disease progression, improve HRQoL, and prolong life. The patient and clinician groups highlighted the lack of treatment options other than cytotoxic IV treatments after first-line chemotherapy and noted that the majority of patients are left with only second-line systemic therapy. The authors of the REGOBONE trial highlighted the significance of the 16-week PFS observed in the regorafenib treatment group. They deemed this duration clinically important, referencing the Pediatric Oncology Group's guidelines.[9] According to these guidelines, a PFS longer than 4 months is considered a positive outcome for single-arm phase II trials involving patients with measurable metastatic or unresectable osteosarcoma. The clinical experts consulted for this review also considered that the magnitude of the observed effect of regorafenib on PFS represents a clinically important improvement in PFS. On the other hand, the 2 trials do not provide evidence that regorafenib improves OS compared to placebo because the reported median CIs were large and overlapping. The SARC024 trial showed no difference in median OS, and REGOBONE was a noncomparative trial, which did not test for significance across treatment arms. In addition, the effect of regorafenib on HRQoL is unknown because this outcome was not measured in either trial.

Both trials compared regorafenib to placebo. In addition to placebo, other relevant comparators of interest for this review (i.e., treatments that are currently reimbursed by at least 1 public drug plan in Canada) included ifosfamide with or without etoposide, cyclophosphamide and topotecan, and gemcitabine with or without docetaxel. The lack of evidence comparing regorafenib to these treatment options represents a gap in the evidence. However, these treatment options are cytotoxic IV (chemotherapy) treatments. Therefore, for patients who have contraindications to these agents or who cannot tolerate further chemotherapy after first-line chemotherapy, there are no other treatment options. Another gap in the evidence is with respect to the pediatric population, given that neither of the trials was able to recruit patients under the age of 18 years.

Harms

In both trials, AEs were more frequent among patients treated with regorafenib compared to those who received placebo. The clinical experts indicated that the AEs are consistent with the mechanism of action of regorafenib and can be managed in most cases with dose reductions. The clinical experts consulted for this

review indicated that hand-foot syndrome, mucositis, hypertension, rash, and cytopenia were some of the AEs that should be monitored in patients treated with regorafenib. Both trials reported a higher frequency of these AEs among patients treated with regorafenib. In SARC024, 8 patients (36%) in the regorafenib arm experienced hand-foot reactions compared to no patients in the placebo arm. In REGOBONE, 5 patients had dose reductions following hand-foot syndrome. In both trials, most AEs were managed with dose reductions. In the SARC024 trial, 59% of patients initially assigned to regorafenib had a dose reduction.

Conclusion

Current treatment options for patients with metastatic osteosarcoma who have received at least 1 prior therapy are limited to further systemic therapies, presenting a challenge for patients who have contraindications to these agents or who are unable to tolerate further chemotherapy, which represents an unmet need for alternative therapeutic options in this patient population. The evidence from 2 randomized phase II trials comparing regorafenib with placebo in patients with metastatic osteosarcoma, who have received at least 1 prior line of systemic therapy, suggests that regorafenib may extend PFS. However, there is no evidence that it improves OS. Additionally, the effect of regorafenib on HRQoL compared to placebo remains uncertain. There were no direct or indirect comparisons of regorafenib to other comparators used in the second- and subsequent-line setting for metastatic osteosarcoma.

Economic Evidence

The economic review consisted of a cost comparison for regorafenib compared with ifosfamide plus etoposide, cyclophosphamide plus topotecan, and docetaxel plus gemcitabine for the treatment of adult and pediatric patients with metastatic osteosarcoma who have received and whose disease has progressed on at least 1 prior line of therapy.

Per 28-day cycle, based on wholesale list prices, regorafenib is expected to have a per-patient cost of $6,100 (Supplemental Material, Appendix 3, Table 3), ifosfamide plus etoposide is expected to have a per-patient cost of $4,084, cyclophosphamide plus topotecan is expected to have a per-patient cost of $4,419, and docetaxel plus gemcitabine is expected to have a per-patient cost of $3,423. The incremental cost of regorafenib compared with ifosfamide plus etoposide, cyclophosphamide plus topotecan, and docetaxel plus gemcitabine is $2,016, $1,681, and $2,677 per patient per 28 days, respectively. As such, the reimbursement of regorafenib for the treatment of patients with metastatic osteosarcoma is expected to increase overall drug acquisition costs. Additional items for consideration are provided in the following bullets:

- Evidence from the REGOBONE[6] and SARC024[7] trials suggests that compared to placebo, treatment with regorafenib may result in longer PFS and higher partial response rates. However, its impact on OS remains uncertain, and its effects on HRQoL are unknown. AEs were more frequent in the regorafenib group of both trials. Regorafenib has not been compared to active comparators in the second- or subsequent-line treatment of metastatic osteosarcoma; therefore, its efficacy relative to ifosfamide plus etoposide, cyclophosphamide plus topotecan, and docetaxel plus gemcitabine is unknown.

- The patent for regorafenib is expected to expire in August 2025.[10] At the time of this review, 2 submissions for generic products were under review by Health Canada.[11] As such, 1 or more generic versions of regorafenib may become available. According to the pan-Canadian Pharmaceutical Alliance Tiered Pricing Framework, after 3 months of funding, a single source generic reduces to 55% of the brand reference price.[12] Assuming a price consistent with 55% of the price of the reference brand, the cost of generic regorafenib would be $3,355 per 28-day cycle, which would be less expensive than its comparator regimens at wholesale list prices. If more than 1 generic product becomes available, the cost of regorafenib would be further reduced.
- According to clinical expert input obtained by CDA-AMC, other TKIs, such as cabozantinib, pazopanib, and sorafenib, can be used to treat osteosarcoma, but such regimens are not currently publicly funded. The estimated per-patient cost of treatment for these comparators ranges from $3,468 to $8,436 per 28 days.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on November 5, 2024.

Conclusion

The reimbursement of regorafenib for the treatment of adult and pediatric patients with metastatic osteosarcoma who have received and progressed on at least 1 prior line of therapy is expected to increase overall drug acquisition costs. Based on the Clinical Review conclusions, compared to placebo, regorafenib may extend PFS, although there was no evidence that it improves OS. There were no direct or indirect comparisons of regorafenib with active regimens used in the second- and subsequent-line setting for metastatic osteosarcoma; as such, the comparative efficacy of regorafenib versus identified comparators is unknown.

Given that regorafenib is associated with increased drug acquisition costs and unknown benefit relative to ifosfamide plus etoposide, cyclophosphamide plus topotecan, or docetaxel plus gemcitabine, reimbursement of regorafenib will add costs to the public health care system with unknown benefit. Therefore, there is insufficient evidence to support a price premium for regorafenib over other treatments used in the second- and subsequent-line setting for metastatic osteosarcoma. Should 1 or more generic versions of regorafenib become available, its treatment cost may be lower than that of its comparators at list prices.

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