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CADTH Reimbursement Recommendation

Entrectinib (Rozlytrek)

Indication: For the treatment of adults with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation and with no satisfactory treatment options

Sponsor: Hoffmann-La Roche Ltd.

Recommendation: Reimburse with conditions

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Rozlytrek?

CADTH recommends that Rozlytrek be reimbursed by public drug plans for the treatment of adults with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation if certain conditions are met.

Which Patients Are Eligible for Coverage?

Rozlytrek should only be reimbursed to treat patients who have previously failed on all standard treatments for their current tumour site and who will be able to tolerate the treatment.

What Are the Conditions for Reimbursement?

Rozlytrek should only be reimbursed as a single-agent therapy and should not be initiated in patients who have primary CNS tumours or those who have received prior treatment with an *NTRK* inhibitor.

Why Did CADTH Make This Recommendation?

Evidence demonstrated that Rozlytrek improves disease control, has a manageable toxicity profile, and may meet the needs of patients with no other effective treatment options. Based on CADTH's assessment of the health economic evidence, Rozlytrek does not represent good value to the health care system at the public list price. A price reduction is therefore required. Based on public list prices, Rozlytrek is estimated to cost the public drug plans approximately $154 million over the next 3 years if testing costs are included. If testing costs are excluded, the budget impact drops to approximately $31 million over the next 3 years.

Additional Information

What Is a Solid Tumour With an *NTRK* Gene Fusion?

Solid tumours with an NT*RK* gene fusion are cancers that produce a protein called tropomyosin receptor kinase that speeds up tumour growth. *NTRK* fusions have been reported in many different types of solid tumours, including sarcomas and breast, colorectal, gynecological, bile duct, pancreas, lung, brain, salivary gland, and thyroid cancers, with the frequency of *NTRK* gene fusion varying across these tumour types.

Unmet Needs in Patients With *NTRK*-Positive Solid Tumours

There are no effective treatments for patients with advanced or metastatic extracranial solid tumours who have an N*TRK* gene fusion and who have previously failed on all standard treatments for their current tumour site. Jurisdictions may need to consider a common approach to *NTRK* fusion–testing strategies to ensure equitable patient access.

How Much Does Rozlytrek Cost?

Treatment with Rozlytrek is expected to cost approximately $8,008 per patient per 28 days.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that entrectinib be reimbursed for the treatment of adult patients with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

A pooled analysis of 3 open-label, single-arm trials (N = 121 and N = 193 for the efficacy and safety populations, respectively) demonstrated that entrectinib-treated adults with extracranial solid tumours (excluding primary central nervous system [CNS] tumours) that harbour an *NTRK* gene fusion exhibited a clinically important objective response rate (ORR) of 61.2% (95% confidence interval [CI], 51.9% to 69.9%). The median time to response was 1 month (95% CI, 0.9 to 1.0), and the median duration of response (DOR) was 20 months (95% CI, 13.0 to 38.2). Among patients with CNS metastases at baseline (N = 19), the intracranial ORR was 52.6% (95% CI, 28.9% to 75.6%), with a median intracranial DOR of 17.2 months (95% CI, 7.4 to not estimable [NE]). There was considerable heterogeneity in the antitumour activity of entrectinib on tumours in different sites and substantial uncertainty in the magnitude of the observed response rate and longer-term effects of entrectinib on patients' survival and health-related quality of life (HRQoL). However, the committee acknowledged that tumours with an *NTRK* gene fusion are rare, which makes the collection of evidence particularly challenging; the correspondingly small numbers of patients in the included studies contributes to the uncertainty in the clinical evidence available to assess the effects of entrectinib.

pERC also considered that the patients for whom entrectinib is indicated often have a substantial burden of disease and no other treatment options. Although the response to entrectinib treatment varied considerably across different tumour sites, pERC evaluated the available evidence from a tumour-agnostic perspective. pERC concluded that the benefits demonstrated in certain types of tumours outweighed the absence of definitive clinical evidence in other tumour types. pERC also noted that entrectinib may meet the needs of patients with no other effective therapeutic options because it can control disease symptoms, provides disease control, has a manageable toxicity profile, and is relatively easy to administer.

Using the sponsor-submitted price for entrectinib and publicly listed prices for all other drug costs, the pooled incremental cost-effectiveness ratio (ICER) for entrectinib was $1,272,991 per quality-adjusted life-year (QALY) gained compared with standards of care across all relevant tumour types. This ICER assumes no testing costs and no additional treatment costs if the therapy fails. If testing costs are included, then the ICER increases to $16,746,589 per QALY gained. At these ICERs, entrectinib is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained in the Health Canada–indicated population. A price reduction is therefore required.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients should have all of the following: 1.1. unresectable locally advanced or metastatic extracranial solid tumours, including patients with brain metastases 1.2. *NTRK* gene fusion 1.3. without a known acquired resistance mutation 1.4. good performance status.	The approved indication for entrectinib is limited to adults with unresectable locally advanced or metastatic extracranial solid tumours who have no satisfactory treatment options. Enrolment in the pivotal studies for entrectinib was limited to patients with good performance status (ECOG performance status of ≤ 2).	pERC noted that *NTRK* fusion testing is not used universally across all public drug programs and cancer agencies in Canada. Because testing methods for detecting *NTRK* fusion are evolving, upon implementation of the reimbursement recommendation, the jurisdictions may need to consider a common approach to define their *NTRK* fusion–testing strategies to ensure equitable patient access and cost-effectiveness (e.g., through health technology assessments of companion diagnostic testing).
2. Reimbursement should be limited to adults (≥ 18 years of age).	Entrectinib is not approved in Canada for use in pediatric patients.	—
3. All available standard treatments for that tumour site should have been previously used and exhausted.	The Health Canada–approved indication for entrectinib is limited to patients who have no satisfactory treatment options.	—
4. Reimbursement with entrectinib should not be initiated in patients who have primary CNS tumours but may be provided for those with controlled or asymptomatic CNS metastases.	The Health Canada–approved indication for entrectinib excludes patients with primary CNS tumours but includes patients with extracranial solid tumours who have CNS metastases.	—
5. Reimbursement with entrectinib should not be initiated in patients who have received prior treatment with an *NTRK* inhibitor.	Patients with prior exposure to an *NTRK* inhibitor were not included in the pivotal studies for entrectinib. There is insufficient evidence to evaluate the efficacy of sequential usage of entrectinib or larotrectinib after disease progression on 1 of the 2 drugs.	—
Renewal		
6. Assessment for renewal of entrectinib should be based on radiographic evaluation (CT and/or MRI): 6.1. every 3 to 4 months for the first year after treatment initiation 6.2. longer interval follow-up may be continued thereafter based on clinical judgment.	This interval is used widely for assessment and radiographic monitoring in oncology. For patients with a sustained response to entrectinib, increasing the imaging interval would be acceptable based on clinical judgment to avoid exposure to radiation.	—

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
7. Reimbursement should be discontinued upon the occurrence of any of the following: 7.1. radiographic disease progression 7.2. unacceptable toxicity.	There is no evidence that re-treatment with entrectinib is effective for patients whose disease has progressed after treatment.	—
Prescribing		
8. Entrectinib should only be prescribed by a clinician experienced in diagnosing and treating patients with *NTRK* gene fusions.	This condition is required to ensure that entrectinib is used in an appropriate care setting.	—
9. Entrectinib should be administered as monotherapy and should not be given in combination with other systemic anticancer therapies.	The trial data were used to evaluate the efficacy and safety of entrectinib as monotherapy.	—
Pricing		
10. A reduction in price.	If testing is required to determine eligibility based on *NTRK* fusion status, then there is no price at which entrectinib could be considered cost-effective at a $50,000 per QALY threshold. This assumes next-generation sequencing testing must be conducted to determine eligibility for entrectinib, and this test would not have been conducted otherwise. If the cost of testing to determine eligibility based on *NTRK* fusion status is excluded from the total treatment cost, then entrectinib would require a price reduction of at least 82% to potentially be considered cost-effective at a $50,000 per QALY threshold. Higher price reductions may be required depending on what therapies are displaced and whether subsequent treatment costs are incurred after treatment with entrectinib. No evidence was presented that suggests entrectinib produces better health outcomes relative to other *NTRK* inhibitors. Therefore, the price of entrectinib should also not exceed that of other *NTRK* inhibitors to ensure cost-effectiveness.	—
Feasibility of adoption		
11. The feasibility of adoption of entrectinib must be addressed.	At the submitted price: • The budget impact of entrectinib is expected to be greater than $40 million in year 3 when the cost of *NTRK* fusion testing	—

Reimbursement condition	Reason	Implementation guidance
	is considered. • The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; NTRK = neurotrophic tyrosine receptor kinase; QALY = quality-adjusted life-year.

Discussion Points

- There was uncertainty with the clinical evidence; therefore, the committee deliberated on entrectinib considering the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. Considering the rarity and severity of the condition, and the absence of clinically effective alternatives, the committee concluded that the available evidence reasonably suggests that entrectinib could substantially reduce morbidity and/or mortality associated with *NTRK* fusion–positive cancers.
- pERC noted that there is uncertainty regarding the line of systemic therapy in which treatment with entrectinib would be most appropriate and recommended that entrectinib be reimbursed for patients if all available standard treatments for that tumour site have been previously used and exhausted. The committee noted that the Health Canada–approved indication for entrectinib is currently limited to patients who "have no satisfactory treatment options"; however, there are no standardized definitions to identify these patients.
- Patient group input to CADTH identified an unmet need in the treatment of adults with *NTRK* fusion–positive tumours who have no satisfactory options. These patients would benefit from a less toxic and less invasive treatment. pERC agreed that entrectinib aligns with patient values because it improves symptom control, provides disease control, has a manageable toxicity profile, and provides patients with ease of administration as an oral therapy.
- There are many tumour sites where NGS testing is not part of standard clinical practice, including those that have a low incidence of *NTRK* fusion. When implementing the reimbursement recommendation, the jurisdictions may need to consider a common approach to define their *NTRK* testing strategies to ensure equitable patient access and cost-effectiveness.
- pERC discussed the pharmacoeconomic analyses and noted that expanded access to *NTRK* fusion testing would be a substantial cost to the health care system. When factoring in the cost of *NTRK* fusion testing, CADTH estimated the 3-year budgetary impact of reimbursing entrectinib to be as high as $154,018,431 (assuming no displacement of other therapies).
- pERC noted there is considerable heterogeneity of cost-effectiveness across tumour sites because of differences in comparators, treatment response effects, survival, and the prevalence of *NTRK* fusion. Because of the rarity of *NTRK* fusion in some more common cancers, there would be considerable cost in simply identifying eligible patients.

Cost-effectiveness could be improved, and the budget impact reduced, if entrectinib was restricted to certain patient populations.

- pERC noted that the available evidence supports antitumour activity, although there was varying degrees of response across the different tumour types included in the pooled analysis. Some tumour types were underrepresented in the pooled analysis population because of the rare nature of the *NTRK* fusion–positive solid tumours, resulting in wide confidence intervals and larger uncertainty around the magnitude of benefit from entrectinib across all tumour sites. However, pERC agreed that subgroup analyses by tumour type were exploratory and hence non-inferential.
- pERC discussed the results of an intraperson growth modulation index (GMI) analysis which suggested that the time to disease progression was longer for patients after they initiated treatment with entrectinib compared with their last prior treatment. pERC noted that the results are supportive of an antitumour effect for multiple different cancers; however, the analysis has many important limitations that prevent drawing definitive conclusions regarding the uniform effectiveness of entrectinib.
- pERC discussed the sponsor's exploratory efficacy analyses comparing entrectinib-treated patients from the clinical trials with patients treated under standard of care from the Flatiron/FMI clinico-genomic database. Important limitations with this analysis, including the small sample size (i.e., [redacted]) and heterogeneity across treatment groups (e.g., matching was based on [redacted] patient characteristics), prevent drawing firm conclusions.
- pERC noted that there is a lack of information on the impact of entrectinib treatment on HRQoL. The analyses in the development program were limited by the open-label administration of the drug, lack of a comparator group, absence of statistical testing, high dropout rates at later assessment time points, and the very small sample size for the disease-specific instruments (e.g., non–small cell lung cancer [N = 12] and metastatic colorectal cancer [N = 7]).
- pERC discussed the adverse events associated with entrectinib, noting the relatively high proportion of patients who experienced cognitive impairment in the pooled safety analysis (27% any grade; 4.5% grade ≥ 3). The product monograph recommends that patients should be counselled regarding the potential for cognitive changes and monitored for signs of cognitive changes or other CNS events while receiving treatment with entrectinib. The product monograph provides recommendations for interrupting or discontinuing treatment as a result of cognitive adverse events.

Background

Entrectinib is an inhibitor of tyrosine receptor kinases A, B, and C (TRKA, TRKB, and TRKC) (encoded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively), proto-oncogene tyrosine-protein kinase ROS (ROS1; encoded by the gene *ROS1*), and anaplastic lymphoma kinase (ALK; encoded by the gene *ALK*). Entrectinib is indicated for the treatment of adult patients with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have an *NTRK* gene fusion without a known acquired resistance mutation, and with no satisfactory treatment options. Entrectinib received Notice of Compliance with conditions (NOC/c) for this indication on February 10, 2020, from Health Canada pending the results of new information to verify its clinical benefit. The sponsor's reimbursement request is per the Health Canada–approved indication.

The product monograph states that a validated assay is required for the selection of patients with *NTRK* fusion–positive unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases. *NTRK* fusion–positive status should be established before initiation of entrectinib therapy.

Entrectinib is available as 100 mg and 200 mg capsules. The recommended dose is 600 mg orally once daily. From the starting dose of 600 mg once daily, the dose can be reduced twice if needed to manage adverse events (e.g., first to 400 mg once daily and then to 200 mg once daily). It is recommended in the product monograph that patients are treated until disease progression or unacceptable toxicity. Health Canada has not authorized an indication for entrectinib for pediatric use, and there are no recommendations in the product monograph regarding dosing in pediatrics.

Sources of Information Used by the Committee

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

- a clinical review of a pooled analysis from 3 multi-centre, open-label, single-arm trials of entrectinib in adults with advanced or metastatic solid tumours: ALKA (phase I), STARTRK-1 (phase I), and STARTRK-2 (ongoing phase II basket trial); additional studies are included to examine important gaps in the evidence, including 1 indirect comparison of entrectinib versus larotrectinib, 1 intrapatient comparison of entrectinib versus traditional comparator treatments, and 1 comparison of entrectinib versus standard of care
- patients' perspectives gathered by 4 patient groups: the Ontario Lung Association or Lung Health Foundation, Lung Cancer Canada, Colorectal Cancer Canada, and the Canadian Breast Cancer Network
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 3 clinical specialists with expertise in diagnosing and treating adults with unresectable locally advanced or metastatic extracranial solid tumours
- input from 5 clinician groups, including Lung Cancer Canada and the Lung Cancer, Breast Cancer, Gastrointestinal Cancer, and Head, Neck, and Thyroid Cancer Drug Advisory Committees from Ontario Health – Cancer Care Ontario
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to entrectinib from published literature.

Ethical Considerations

The literature on ethical issues related to tumour-agnostic therapies and their evaluations of effectiveness via basket trials, and the use of genetic testing (companion diagnostic or otherwise) to identify people living with *NTRK* fusion–positive solid tumours were reviewed to identify ethical considerations related to the use of entrectinib.

- Ethical issues identified in the context of genetic testing for *NTRK* fusion–positive solid tumours included questions regarding the validity and utility of the genetic tests being used to identify *NTRK* gene fusions, accessibility or availability of these tests, and considerations regarding resource allocation and costs of genetic testing.
- Ethical issues identified regarding the application of basket trials using master protocols to evaluate the effectiveness of tumour-agnostic therapies included challenges to their scientific validity and the potential for undue risks to clinical trial participants. The literature identified that scientific validity could be affected by assumptions about a single treatment for a single biomarker in tumours that may have heterogenous molecular aberrations, the absence of comparative data, issues related to publication bias given master protocols open-ended inclusion and exclusion criteria, and insufficient trial participation or diversity of trial participants. Challenges identified in relation to the potential for undue risks to research participants in relevant clinical trials included those about the balance between risks and benefits and the ability to achieve valid informed consent.

Stakeholder Perspectives

Patient Input

Four patient groups provided input into CADTH's review: the Ontario Lung Association or Lung Health Foundation; Lung Cancer Canada; Colorectal Cancer Canada; and the Canadian Breast Cancer Network. All of the groups obtained information to support their input through surveys. Patient groups expressed the need for treatments that could extend progression-free survival (PFS), delay disease progression, relieve cancer-related symptoms, improve quality of life, and minimize side effects from treatment. Also, patients wish to reduce the impact of cancer on their ability to care for children and dependents, continue working, spend time with loved ones, participate in social activities, travel, maintain friendships, and pursue personal interests. Similar to the clinicians who provided input to CADTH, the patient groups highlighted inconsistency across Canadian jurisdictions with access to *NTRK* fusion testing. Patients emphasized a desire for *NTRK* fusion testing to be available earlier with the hope of avoiding exposure to alternative treatments that may be less effective and associated with more adverse events than an *NTRK*-targeting therapy. The input from 3 patient groups included information documenting the positive experience of patients with 3 different cancer types who had *NTRK* gene fusion and received treatment with entrectinib.

Clinician Input

Input From Clinical Experts Consulted by CADTH

A panel of 3 clinical oncologists from across Canada provided input for this review. Because entrectinib is approved for use in a manner that is independent of tumour histology (with the exception of primary CNS tumours), each of the clinicians on the review team has expertise in the diagnosis and management of different types of primary tumours. The clinicians consulted by CADTH felt that it was difficult to fully characterize the unmet need for patients who could be eligible for treatment with entrectinib. This is due to the breadth of potential advanced solid tumours that may harbour *NTRK* fusion mutations and variability with the availability and effectiveness of potential alternative therapies. However, they agreed that, in the case of metastatic solid malignancies, virtually all patients eventually progress

on currently available therapies, with the possible exception of select patients receiving immunotherapies for select cancer types.

The clinicians noted that the appropriateness of recommending that patients try other treatments before initiating treatment with entrectinib would depend on the cancer subtype and efficacy of front-line therapy. Similar to the patient group input, the clinical experts consulted by CADTH agreed that *NTRK*-targeting therapies, such as entrectinib, should be considered early in the course of *NTRK* fusion cancer treatment. This was based on the following rationale:

- entrectinib may be associated with higher response rates, have a better safety profile, and be more tolerable than existing alternatives
- given its mechanism of action and the available evidence, the clinical experts believed that entrectinib would be efficacious in patients with *NTRK* gene fusions and advanced disease, regardless of the number of prior therapies
- patients may no longer be fit for any systemic therapy after receiving alternative treatments (e.g., poor performance status)
- the presence of *NTRK* fusion mutations is clinically actionable and the Canadian consensus guidelines recommend the use of *NTRK* inhibitors as the preferred option for patients with *NTRK* fusion tumours.

Treatments targeting the tumour as opposed to the *NTRK* fusion may be less effective and potentially more toxic than an *NTRK*-targeted therapy (i.e., entrectinib or larotrectinib), particularly for tumours for which the alternative is chemotherapy. All clinicians noted that there is considerable variability with access to NTRK fusion testing across tumour sites and across different Canadian jurisdictions. A targeted therapy, such as entrectinib, would be identified as a potential treatment option depending on whether the tumour is routinely tested for *NTRK* fusion and the timing of the testing.

The clinicians noted that, in adults, objective response, non-progression, patient-reported improvements in their ability to perform activities, improved survival, stabilization, improvement or reduced severity of symptoms, and improvement or no deterioration in quality of life would all be considered clinically meaningful outcomes. Clinicians noted that treatment response is typically assessed every 3 months; this interval may be prolonged once response is established or remission is achieved. The clinicians noted that treatment failure would be determined by disease progression, treatment intolerability, poor quality of life (e.g., poor performance status), or patient request to discontinue treatment.

Clinician Group Input

Five clinician groups provided input for this review, including Lung Cancer Canada and the Lung Cancer, Breast Cancer, Gastrointestinal Cancer, and Head, Neck, and Thyroid Cancer Drug Advisory Committees from Ontario Health – Cancer Care Ontario. The input from the clinician groups was similar to the input from the clinical experts consulted by CADTH with respect to the unmet medical needs for adults with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have an *NTRK* gene fusion without a known acquired resistance mutation and with no satisfactory treatment options. The clinician groups also noted that the place in therapy for entrectinib would vary depending on the tumour site and the availability of safe and effective alternative therapies and the timing of access to *NTRK* fusion testing. Input regarding important end points, timing

and criteria for evaluation, and likely discontinuation criteria were the same as the experts consulted by CADTH.

Drug Program Input

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

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- system and economic issues.

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The pivotal entrectinib studies included patients with CNS metastases that were previously treated and/or asymptomatic. For patients with *NTRK* fusion–positive solid tumours and CNS metastases, is there a preferred *NTRK* inhibitor (e.g., larotrectinib vs. entrectinib)?	pERC noted that the clinical experts consulted by CADTH stated that, based on the limited available data, entrectinib may have more CNS penetration and promising intracranial activity for those patients with brain metastases. However, additional data and longer-term follow-up would be required to establish any conclusions regarding the comparative effectiveness of entrectinib and larotrectinib for patients with CNS metastases.
How do the efficacy and safety of entrectinib compare to best supportive care for patients with unresectable locally advanced or metastatic solid tumours with confirmed *NTRK* fusion–positive disease who have exhausted all other therapies?	pERC agreed with the clinical experts that entrectinib-treated adults with *NTRK* gene fusion–positive tumours had a clinically meaningful response rate that would not be expected in patients treated with best supportive care, although there is a lack of comparative efficacy data. Entrectinib is associated with manageable toxicities. Input from clinician groups and the clinical experts consulted by CADTH noted that entrectinib should be considered early during *NTRK* fusion cancer treatment. This was based on the rationale that the *NTRK* fusion is the oncogenic driver in these tumours. Treatments targeting the tumour as opposed to the *NTRK* fusion may be less effective and potentially more toxic than *NTRK*-targeting therapies, particularly for tumours for which the alternative is chemotherapy.
How do the efficacy and safety of entrectinib compare to existing systemic therapies used for treatment of unresectable locally advanced or metastatic solid tumours with confirmed *NTRK* fusion–positive disease in any line of therapy?	pERC noted that the clinical experts consulted by CADTH stated that entrectinib would be expected to act in a manner similar to other current histology-specific targeted agents (such as ALK or EGFR). This is based upon data that demonstrates that patients with *NTRK*-positive cancers do not have better outcomes compared with patients without the mutation, the very high response rates observed with entrectinib and larotrectinib in the presence of an *NTRK* gene fusion, and clinical expert opinion and experience,

Implementation issues	Response
	recognizing that the ORR reported for entrectinib and larotrectinib surpass expected response rates with alternate systemic therapies in advanced diseases.
Considerations for initiation of therapy	
Patients with an ECOG performance status of 2 or less were eligible for the pivotal trials. Should eligibility for treatment with entrectinib be limited to patients with ECOG performance status of 2 or less?	The clinical experts suggested that patients with a higher ECOG performance status could be eligible for treatment with entrectinib if the oncologist believes that tumour-related symptoms are driving the performance status. The rationale is based on the high rate of response, duration of the responses, median time to response (i.e., approximately 1 month), and favourable toxicity profile. pERC appreciates that there are factors, including tumour-related symptoms, that may drive the deterioration in the patient's performance status; however, enrolment in the clinical trials for entrectinib was limited to patients with good performance status.
What is an appropriate definition for "no satisfactory treatment options" for unresectable locally advanced or metastatic solid tumours with confirmed *NTRK* fusion–positive disease?	pERC noted that the clinical experts consulted by CADTH stated that the definition of "no satisfactory treatment options" would depend on the tumour sites and reflect the range of alternative therapies available for those tumours (e.g., some have no alternatives and others may have several alternatives). The clinical experts agreed that "no satisfactory treatment options" would be interpreted by clinicians to mean suboptimal treatment for the patient with respect to achieving treatment goals (e.g., improving survival and disease-free interval) or be associated with poor quality of life and/or significant toxicity.
The funding request for entrectinib is for use in adults with extracranial solid tumours only. Pediatric patients were not included in the funding request nor in the Health Canada approval. Patients with primary CNS solid tumours were not included in the funding request. Is there evidence to inform the use of entrectinib in: • pediatric patients with *NTRK* fusion–positive solid tumours? • in *NTRK* fusion–positive primary CNS tumours?	pERC noted that the sponsor initially sought regulatory approval for an indication that would include use in pediatric patients as well as those with primary CNS tumours. Health Canada did not approve usage in pediatric patients, citing the negative benefit vs. risk profile of entrectinib in the pediatric population, or for use in patients with primary CNS tumours, citing the lack of sufficient efficacy data to support benefit in primary brain tumours.
Considerations for continuation or renewal of therapy	
The STARTRK-2, STARTRK-1, and ALKA trials performed on-treatment tumour assessments via CT or MRI scans at the end of cycle 1 (4 weeks) and at the end of alternate cycles thereafter (i.e., every 8 weeks), or whenever a clinical deterioration was observed, and at end of treatment if not done in the previous 4 weeks. What are clinically appropriate modalities and frequencies to assess therapeutic response to entrectinib?	pERC agreed with the clinical experts consulted by CADTH who advised that, in terms of outcomes that are used to determine whether a patient is responding to treatment in clinical practice, the typical metrics of treatment efficacy include disease evaluation by cross-sectional imaging modalities (MRI, CT, PET/CT) to assess response by RECIST (for solid tumours) or RANO (for CNS tumours), symptom improvement, treatment tolerability, and time to progression. pERC also agreed with the clinical experts that treatment response is typically assessed every 3 months; once response is established or remission is achieved, this interval may be prolonged.

Implementation issues	Response
Considerations for discontinuation of therapy	
The STARTRK-2, STARTRK-1, and ALKA trials permitted dose reductions due to toxicity (up to a maximum of 2 dose reductions) and treatment interruption of up to 28 days due to treatment-related adverse effects. Treatment was discontinued if symptom resolution did not occur. Are the treatment interruption and discontinuation parameters used in the STARKTR-2, STARKTR-1, and ALKA trials applicable to clinical practice?	pERC noted that the product monograph for entrectinib provides detailed recommendations for the management of adverse events that require temporary interruption, dose reduction, or discontinuation of treatment with entrectinib. The clinical experts consulted by CADTH indicated that this is a reasonable reflection of how patients would be managed in clinical practice.

ALK = anaplastic lymphoma kinase; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NTRK = neurotrophic tyrosine receptor kinase; ORR = objective response rate; RANO = response assessment in neuro-oncology; RECIST = Response Evaluation Criteria in Solid Tumours.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The submission for entrectinib was based on a pooled analysis of 3 multi-centre, open-label, single-arm trials of entrectinib in adults with advanced or metastatic solid tumours: ALKA (phase I), STARTRK-1 (phase I), and STARTRK-2 (ongoing phase II basket trial). The primary evaluation for the pooled analysis was based on a clinical cut-off date (CCOD) of May 31, 2018, which was subsequently updated with larger sample sizes and longer follow-up (October 31, 2018, and August 31, 2020). The CADTH report reflects the most recent analysis available (CCOD: August 31, 2020).

The pooled analysis for the August 31, 2020, CCOD consisted of the following datasets:

- NTRK safety-evaluable population (N = 193): all patients with an *NTRK* fusion–positive tumour who received at least 1 dose of entrectinib
- NTRK efficacy-evaluable population (N = 121; 98% from STARTRK-2): all patients with *NTRK* fusion–positive extracranial primary tumours who received at least 1 dose of entrectinib, had measurable disease at baseline, and at least 12 months of follow-up
- NTRK efficacy-evaluable population with CNS metastases at baseline (N = 19 based on blinded independent review committee [BIRC] assessment): this subpopulation was used for the evaluation of the "intracranial efficacy" end points.

Nearly all patients in the pooled analysis were from the STARTRK-2 trial in which patients received entrectinib at the dosage recommended in the Canadian product monograph (i.e., starting dosage of 600 mg once daily with up to 2 dose reductions permitted to manage adverse events).

The primary outcomes in the pooled analysis were ORR, defined as the proportion of patients with a best overall response of either complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumours 1.1 (RECIST Version 1.1) and determined by a BIRC; DOR; and best objective response. Secondary efficacy end points in the pooled analysis included time to tumour response; clinical benefit rate, defined

as the proportion of patients with CR, PR, or stable disease for at least 6 months; PFS; and overall survival (OS). In addition, the sponsor pre-specified the following intracranial efficacy end points that were evaluated in the pooled subset of patients who had CNS metastases at baseline: intracranial ORR, intracranial DOR, and intracranial PFS. HRQoL data were only evaluated in the STARTRK-2 trial and included change from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), EORTC QLQ-LC13 for the subset of patients with non–small cell lung cancer (NSCLC), and the EORTC QLQ-CR29 for the subset of patients with metastatic colorectal cancer.

The NTRK efficacy-evaluable analysis set (N = 121) was 51.2% female with a mean age of 55.9 years (64.5% were younger than 65 years). The baseline ECOG performance status was 43.8% for 0, 47.1% for 1, or 9.1% for 2. The majority of patients had received some form of prior anticancer therapy (n = 97; 80.2%); 74 (61.2%) patients had received any prior radiotherapy and 103 (85.1%) patients had previous cancer surgery. Approximately 30.6% of patients did not have prior systemic anticancer therapy. For those with a history of prior systemic therapy, 28.9% had 1 line, 21.5% had 2 lines, 9.9% had 3 lines, and 5.8% had 4 lines of systemic therapy. The most frequent systemic prior anticancer therapy was chemotherapy (n = 88; 72.7%), followed by targeted therapy (n = 24; 19.8%), immunotherapy (n = 13; 10.7%), and hormonal therapy (n = 10; 8.3%).

The solid tumour types that were reported for at least 5% of the patients included sarcoma (n = 26; 21.5%), mammary analogue secretory carcinoma (n = 24; 19.8%), NSCLC (n = 22; 18.2%), thyroid cancer (n = 13; 10.7%), colon cancer (n = 10; 8.3%), and breast cancer (n = 7; 5.8%). Nearly all patients had metastatic disease at baseline (96.7%); the most common metastatic sites were lung (61.2%) and lymph nodes (55.4%). There were 19 (17.2%) patients with CNS metastases at baseline as assessed by BIRC, with 17 (14.0%) patients reporting prior radiotherapy of the brain.

Efficacy Results

Unless otherwise noted, the efficacy results are from the August 2020 CCOD.

ORR: In the NTRK efficacy-evaluable dataset, the ORR by BIRC was 61.2% (95% CI, 51.87% to 69.88%). A best objective response of CR or PR was demonstrated by 15.7% and 45.5% of patients, respectively. The point estimates for ORR ranged widely across tumour types and the Cis reflected a high degree of uncertainty for many tumour types. At least 1 patient demonstrated a response to treatment in each of the tumour types, with the exception of neuroblastoma (n = 1). The ORR for the larger subgroup populations were generally consistent with the results for the overall population; though a higher proportion of tumour response was reported for the patients with salivary mammary analogue secretory carcinoma tumours (20 of 24; 83.3% [95% CI, 62.6% to 95.3%]) and a lower proportion for those with colorectal carcinoma (2 of 10; 20% [95% CI, 2.5% to 55.6%]).

Intracranial ORR: The BIRC-assessed intracranial ORR was 52.6% (95% CI, 28.86% to 75.55%) and 63.6% (95% CI, 30.8% to 89.1%) for all patients with baseline CNS disease (10 of 19 responded) and those with measurable disease at baseline (7 of 11 responded), respectively. A subgroup analysis demonstrated similar results for those who had no prior brain radiotherapy or brain radiotherapy at least 6 months before the initiation of treatment (55.6%; 95% CI, 21.2% to 86.3%; n = 9) and those with prior brain radiotherapy within 6 months of initiating treatment with entrectinib (50.0%; 95% CI, 18.7% to 81.3%; n = 10).

Time to tumour response: The median time to objective response was 1.0 month (95% CI, 0.9 to 1.0) for the overall population and 1.3 months (95% CI, 0.9 to 2.8) for patients with CNS metastases at baseline.

DOR: The DOR among responders was 20.0 months (95% CI, 13.0 to 38.2). For the patients who demonstrated a CR or PR with entrectinib, responses that lasted at least 6, 12, 18, 24, 30, and 36 months were reported for 58 (78%), 46 (62%), 32 (43%), 20 (27%), 10 (14%), and 4 (5%) of patients. The event-free probability was 0.82 (95% CI, 0.73 to 0.91) at 6 months, 0.66 (95% CI, 0.55 to 0.77) at 12 months, 0.49 (95% CI, 0.37 to 0.61) at 24 months, and 0.39 (95% CI, 0.24 to 0.53) at 36 months.

Intracranial DOR: The intracranial DOR among responders was 17.2 months (95% CI, 7.4 to NE) and 22.1 months (95% CI, 7.4 to NE) for all patients with baseline CNS disease and those with measurable disease at baseline, respectively.

Clinical benefit rate: The clinical benefit rate was 63.6% (95% CI, 54.8% to 71.7%).

PFS: The median PFS was 13.8 months (95% CI, 10.1 to 19.9), with a total of 72 (59.5%) patients experiencing disease progression or death at the CCOD of August 31, 2020. Updated subgroup analyses for PFS were not reported for the August 2020 CCOD.

Intracranial PFS: The median PFS was 10.1 months (95% CI, 6.3 to 26.7) with a total of 13 (68.4%) patients experiencing CNS disease progression or death at the August 2020 CCOD (5 progressive disease [PD] events and 8 deaths).

OS: The median OS was 33.8 months (95% CI, 23.4 to 46.4), and a total of 49 (40.5%) patients had died by the August 2020 CCOD. For patients with CNS metastases at baseline, the median OS was 19.9 months (95% CI, 7.9 to NE), with 50.2% patients having died by the August 2020 CCOD.

Harms Results

Nearly all *NTRK* fusion–positive patients experienced at least 1 adverse event (99.5%), 46.1% of patients experienced at least 1 serious adverse event, and 69.4% of patients experienced at least 1 grade 3 or higher adverse event. The proportion of patients with an adverse event leading to dose interruption or dose reduction was 54.4% and 26.9%, respectively. The proportion of patients with an adverse event leading to discontinuation was 14.5%.

The product monograph for entrectinib provides detailed recommendations for the management of adverse events that require temporary interruption, dose reduction, or discontinuation of treatment with entrectinib. The clinical experts consulted by CADTH indicated that those recommendations are a reasonable reflection of how patients would be managed in clinical practice. The product monograph also includes black box warnings that the drug may cause congestive heart failure and may cause fetal harm when administered to a pregnant woman. The clinical experts consulted by CADTH noted that patients would likely be screened and monitored for risk factors and symptoms related to heart failure before treatment and during follow-up visits while on treatment. Overall, the clinical experts consulted by CADTH agreed that the safety and tolerability of entrectinib was reasonable.

Critical Appraisal

Internal Validity

Due to the rarity of *NTRK* fusion cancers, the sponsor conducted pooled analyses of efficacy and safety for the basis of the regulatory and reimbursement review submissions. Although the pooled analyses included patients from 3 trials, nearly all of the patients were from the STARTRK-2 trial (98% and 97% in the efficacy and safety analyses sets, respectively). This reduces the potential uncertainty that can arise from between-study heterogeneity (e.g., differences in study design, objectives, phases, outcome measures, and eligibility criteria across trials) that was previously noted by CADTH for larotrectinib. Despite the use of pooled analyses, the sample sizes for each individual cancer type were too small, as would be expected due to the low prevalence of *NTRK* gene fusions (9 of 14 tumour types contained fewer than 10 patients), and the consequent 95% CIs were too wide to evaluate the consistency of the effect of entrectinib on different tumour types.

The efficacy end points were evaluated using BIRC-assessed outcomes for the primary analyses (with investigator-assessed outcomes provided as a sensitivity analysis); this is an important design feature because the trials were all open-label, single-arm studies. DCR, PFS, and OS are important end points for evaluating the efficacy of cancer treatments; however, these cannot be interpreted in the absence of a control group. In addition, a number of survival outcomes (PFS, OS, and DOR) were analyzed using the Kaplan-Meier method to pool data across the 3 trials, which could be problematic because traditional survival analysis methods, such as Kaplan-Meier curves, rely on the assumption that a single survival distribution can be used to estimate the survival outcome for all patients included in the analysis. However, as noted previously, nearly all the patients were derived from a single trial (STARTRK-2), thereby limiting concerns about the pooled approach for survival analyses. The HRQoL analyses were conducted for only 1 of the trials (STARTRK-2) and were limited by the open-label administration of entrectinib, lack of comparator group, absence of statistical testing, and small sample size for the disease-specific instruments for patients with NSCLC (N = 12) and metastatic colorectal cancer (N = 7).

External Validity

The patient population in the pooled analysis was considered to be a reasonable reflection of the target population in Canada (i.e., adults with *NTRK* fusion–positive, unresectable, locally advanced, or metastatic extracranial solid tumours). Not all solid tumour types were represented in the pooled analysis and the majority of tumour types had fewer than 10 patients, resulting in wide CIs within subgroup analyses and reducing confidence in the generalizability of the results. Patients included in the pooled analysis had an ECOG performance status of 0, 1, or 2. Nearly all patients in the pooled analysis received entrectinib at the dosage recommended in the Canadian product monograph (i.e., starting dosage of 600 mg once daily with up to 2 dose reductions permitted to manage adverse events).

There were no direct or indirect comparisons filed by the sponsor to evaluate the comparative efficacy and safety of entrectinib versus larotrectinib or other alternative therapies.

Indirect Comparisons

No studies have directly compared entrectinib versus larotrectinib for patients with *NTRK*-positive tumours. The sponsor did not include an indirect comparison in their application to CADTH because they did not think it feasible to conduct a meaningful comparison due to the following challenges: *NTRK* fusions are only expressed in up to 1% of all solid tumours;

patient enrolment in trials is low; and ongoing trials are single-arm, open-label, and with a study population with heterogeneous baseline characteristics (e.g., age, ECOG performance status, tumour site, presence of CNS metastases). In the absence of direct or indirect evidence comparing entrectinib and larotrectinib in the submission, CADTH conducted a literature search to identify any relevant published indirect comparisons and identified 1 matching-adjusted indirect comparison (MAIC) that compared entrectinib and larotrectinib in adults with *NTRK* gene fusion–positive tumours.

Description of Studies

Garcia-Foncillas et al. (2022) conducted an MAIC to compare the efficacy and safety of entrectinib and larotrectinib in adults with *NTRK* fusion–positive tumours. The MAIC was funded by the manufacturer of larotrectinib; therefore, patient-level data were available for the larotrectinib-treated patients but not for entrectinib-treated patients. The data used for entrectinib were derived from the earlier May 31, 2018, and October 31, 2018, CCODs (i.e., a smaller sample size than the August 31, 2020, CCOD data included in the current submission to CADTH). Adult patients were selected for inclusion in the MAIC based on the presence of *NTRK* fusion, an ECOG performance status of 2 or less, and were *NTRK* inhibitor-naive. Patients were matched on the following baseline characteristics: sex, age, race, ECOG performance status, tumour type, metastatic disease (versus locally advanced, unresectable disease), *NTRK* fusion type, prior lines of systemic therapy for metastatic disease, and CNS metastases.

Efficacy Results

Garcia-Foncillas et al. (2022) reported that larotrectinib was associated with a statistically significantly greater duration of OS (hazard ratio [HR] = 0.43; 95% CI, 0.23 to 0.83; P < 0.05) and DOR (HR = 0.49; 95% CI, 0.25 to 0.98; P < 0.05) compared with entrectinib. The authors reported no statistically significant difference for PFS (HR = 0.66; 95% CI, 0.42 to 1.03; P = 0.07) or ORR (risk difference = 3.8; 95% CI, −11.7 to 19.3; P = 0.63). Results were similar in sensitivity analyses applying different specifications for the MAIC and using a simulated treatment comparison method.

Harms Results

There were no statistically significant differences reported between larotrectinib and entrectinib for serious treatment-related adverse events or treatment-related adverse events leading to discontinuation.

Critical Appraisal

Several key details from the MAIC were not provided in the published study, which limits the ability to provide a critical appraisal. However, the primary limitation of the results is due to the unanchored nature of the comparison, which would require the inclusion of all prognostic factors and all effect modifiers to ensure unbiased results. Therefore, due to this limitation and others, firm conclusions based on the results of this MAIC are not recommended.

Intraperson Growth Modulation Index Analysis

The sponsor provided the intrapatient comparison of efficacy from a single-arm trial of entrectinib in tumour-agnostic indications. The sponsor's objective was to generate and analyze evidence for the comparative effectiveness of entrectinib by exploring the role of intrapatient comparison as an alternative to a traditional comparator arm.

Populations and Methods

Analyses were conducted on retrospectively collected data from the STARTRK-2 trial to generate intrapatient comparisons. There were 3 cohorts of patients based on their prior systemic therapy in the metastatic setting and presence or absence of documented progression.

- Documented progression on prior therapy cohort: patients who received at least 1 systemic therapy for metastatic disease before commencing entrectinib and had clear documentation of PD on the most recent prior therapy, as captured in electronic case report forms.
- No documented progression on prior therapy cohort: patients who received at least 1 systemic therapy for metastatic disease before commencing entrectinib and had no documentation of PD on the most recent prior therapy. This cohort included patients who stopped prior therapy due to toxicity, completion of the course, or other reasons.
- No prior therapy cohort: patients who received no prior systemic therapy for metastatic disease before starting entrectinib, although they may have received prior (neo-) adjuvant therapy.

A total of 71 patients with efficacy-evaluable *NTRK* fusion–positive disease who were enrolled in the STARTRK-2 trial up to April 30, 2018 (data cut-off October 31, 2018), were included in the analysis. Of 71 patients, 51 patients had received systemic therapy before commencing entrectinib (38 had documented PD and 13 had no documented PD on the most recent prior systemic therapy) and 20 patients had not received prior systemic therapy. Among those who had received prior systemic therapy, 21 (41.2%) received 1 line, 20 (39.2%) received 2 lines, and 10 (19.6%) received 3 or more lines of therapy. The treatment regimens varied greatly within and between tumour types. The most common tumour types were sarcoma (22.5%), NSCLC (16.9%), mammary analogue secretory carcinoma (16.9%), and thyroid cancer (9.9%).

The key analysis used was GMI as defined by the ratio of PFS on entrectinib to time to discontinuation (TTD) on the most recent prior therapy. TTD was chosen to measure efficacy of the prior therapy instead of time to progression due to the limited data available to reliably define a time to progression outcome. A GMI ratio of at least 1.3 was selected as the threshold to indicate a clinically meaningful benefit. Additional analyses explored TTD and ORR for entrectinib and prior systemic therapy.

Results

For GMI in patients with PD on prior systemic therapy, median GMI was 2.53 (range, 0.09 to 61.5) with 25 (65.8%) patients having a GMI of at least 1.3. For GMI thresholds, 23 (60.5%) patients met the 1.5 or greater threshold, 23 (60.5%) patients met the 1.8 or greater threshold, and 22 (57.9%) patients met the 2.0 or greater threshold. Of 7 patients with a GMI less than 1.0, 4 (57.1%) patients were censored for PFS.

Kaplan-Meier survival analysis showed that the curves for PFS and TTD for entrectinib were similar (PFS to TTD: HR = 1.08; 95% CI, 0.6 to 1.9), with a median PFS of 11.2 months (95% CI, 6.7 to NE) and a median TTD of 9.9 months (94% CI, 7.3 to 14.8) on entrectinib. Both PFS and TTD on entrectinib were longer than TTD on most recent prior therapy, which was for a median of 2.9 months (95% CI, 2.0 to 4.9). The ORR for entrectinib was 60.5% (23 of 38; all PR) in patients with documented progression on prior therapy, 46.2% (6 of 13; all PR) in patients with no documented progression on prior therapy, and 80% (5 of 20 with CR and 11 of 20 with PR) in patients with no prior therapy.

The ORR for the most recent prior systemic therapy was 15.8% (6 of 38; 1 CR and 5 PR) in patients with documented progression on prior therapy and 7.7% (1 of 13; 1 PR) in patients with no documented progression on prior therapy.

Critical Appraisal

In summary, the results show a longer PFS with entrectinib relative to the TTD with the last prior treatment; however, this observation relies on many assumptions, including the key assumption (TTD as a surrogate for PFS), which appears to be invalid based on the information provided about the calculation of the GMI. There was no formal investigation of differences in the GMI by tumour type or other patient characteristics, and the descriptive individual GMI results suggest large variations in the GMI. It is unclear how some of the presented results were obtained or if inferences made with them are valid given the intrapatient nature of the analysis. However, if the GMI can be considered a reliable comparison tool, it appears to support the case that entrectinib may be beneficial in many of the tumour types when other treatments have failed, which is the case across many patient characteristics, mitigating many of the concerns about patient heterogeneity other than tumour type. Without inference (the presented CI), a large variation in GMI is evident across the tumour types and remains a main limitation.

Exploratory Efficacy Analyses Comparing Entrectinib Against Standard of Care

The sponsor provided a report comparing OS in patients with *NTRK* fusion–positive solid tumours who were treated with entrectinib in the sponsor's clinical trials (pooled dataset) versus patients treated with standard of care from the Flatiron/FMI clinico-genomic database.

Populations and Methods

The Flatiron Health database is a US longitudinal database with de-identified data originating from approximately 280 cancer clinics and representing more than 2.8 million patients with cancer (the majority from community oncology settings). The Flatiron Health data platform aggregates and processes patient-level data.

Median weighted OS, both crude and matched was estimated via Kaplan-Meier survival curves. HRs were estimated using weighted univariate Cox proportional hazards models for patients treated with entrectinib compared with patients not treated with entrectinib. The index date for the end point analyzed was the start of entrectinib treatment for trial patients and the *NTRK* positive test report date for those who received standard of care.

The nearest-neighbour propensity score matching model with replacement was used to perform the matching, with each match first done within each tumour type observed in the *NTRK* fusion–positive population (direct match by tumour). Characteristics included in this analysis were tumour type/histology, age of patient, stage of cancer at diagnosis, number and type of previous treatments, and type of centre where patient was treated (academic versus community).

Patient Characteristics

Before matching, the study population with the same tumour type consisted of [redacted] patients who received standard of care and [redacted] entrectinib-treated patients. Compared with the standard of care group, the entrectinib-treated group were younger (median age: [redacted]), included a higher proportion of women ([redacted]), were treated only in academic

centres, and had a lower proportion of patients with a history of smoking ([redacted]). Standard of care patients were more heavily treated at the index date (e.g., only [redacted] had not received treatment before the index date versus [redacted] of the entrectinib-treated patients) and were more likely to have stage IV disease at the time of initial diagnosis ([redacted]). When the 2 cohorts were matched, the main analyses only included [redacted] trial patients matched to [redacted] standard of care patients, and only a moderate balance of cohorts could be achieved for the 4 variables selected a priori ([redacted]).

Results

[redacted]

Critical Appraisal

The following important limitations prevent drawing firm conclusions based on the results of this analysis:

- The sample size for the comparison was very small, with only [redacted] patients included in the standard of care group. CADTH acknowledges that this is a rare condition; however, this remains an important limitation.
- There was heterogeneity across the entrectinib and standard of care groups even after propensity score matching.
- The groups were only matched based on [redacted] characteristics, which is not sufficient to control for potential confounding factors.
- There were also missing values in relevant covariates, such as ECOG performance status ([redacted]) and the number of metastatic sites (underreported in the Flatiron Health data), which prevented their inclusion in the a priori matching.
- Sample size was too small to allow for exploration by subgroup of tumour types or lines of prior therapy (both identified as subgroups of interest for CADTH's review).
- Unlike those in the standard of care group, patients received entrectinib in a clinical trial setting. The timing of tumour assessment while on entrectinib was controlled through standardized clinical trial protocols, but not when patients were receiving prior therapies outside of the clinical trial setting. RECIST was used to assess entrectinib response, but not for prior therapies. PFS on entrectinib was analyzed by BIRC, whereas TTD on prior therapy was based on investigator assessment.

Summary

The results show a longer median OS with entrectinib compared with patients who received standard of care ([redacted] versus a weighted OS [redacted]). Important limitations with this analysis, including the small sample size and heterogeneity across treatment groups, prevent drawing firm conclusions.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adults with unresectable locally advanced or metastatic extracranial solid tumours, including brain metastases, that have an *NTRK* gene fusion without a known acquired resistance mutation and with no satisfactory treatment options
Treatment	Entrectinib (600 mg orally daily)
Submitted price	Entrectinib, 200 mg capsule, $95.33 Entrectinib, 100 mg capsule, $47.67
Treatment cost	Entrectinib has a 28-day cost of $8,007.72 at a 600 mg daily dose.
Comparators	Comparators for each tumour site analyzed (representing best supportive care including therapies used in first-line and second-line): • breast cancer (secretory): paclitaxel, docetaxel, carboplatin, eribulin • breast cancer (non-secretory): paclitaxel, docetaxel, carboplatin, eribulin • colorectal cancer: pembrolizumab (MSI-H), FOLFOX, FOLFIRI, bevacizumab + FOLFOX • MASC: sunitinib, gefitinib, cisplatin + gemcitabine • lung cancer (squamous) (SCLC): pembrolizumab + carboplatin and paclitaxel/nab-paclitaxel, pembrolizumab, docetaxel • NSCLC: pembrolizumab + pemetrexed and cisplatin, pembrolizumab, pemetrexed + cisplatin, pemetrexed, cisplatin, docetaxel • neuroendocrine: octreotide • pancreatic: FOLFIRINOX, gemcitabine + nab-paclitaxel • soft tissue sarcoma: doxorubicin, imatinib, eribulin • thyroid cancer (papillary): lenvatinib, sorafenib • thyroid cancer (other): doxorubicin, paclitaxel
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Lifetime (10 years)
Key data source	Single-arm entrectinib trials: ALKA (phase I), STARTRK-1 (phase I), and STARTRK-2 (ongoing phase II basket trial) Naive comparison based on literature estimates for comparator PFS and OS; 1 trial selected per comparator. Comparator populations were not selected for *NTRK* fusion status
Key limitations	• Pooled analysis masks the variability in the comparative effectiveness and cost-effectiveness of entrectinib across tumour sites. This in turn masks the patient populations, settings, or conditions for which entrectinib may or may not be cost-effective. • Pooled analysis does not represent the heterogeneity in response, duration of response, PFS, or OS as reported in the clinical report. Sponsor's analysis relied on survival analysis (estimation of PFS and OS curves) performed on a highly heterogeneous population in terms of prognosis, based on tumour site and number of prior lines of therapy, which is inconsistent with the core assumptions of survival analysis

Component	Description
	(requiring a homogeneous study population). The averaging of outcomes across comparators that vary in costs of treatment and prognoses was performed incorrectly because it did not account for the changing composition of the population over time. • Stratified analysis is presented for 6 cancer subtypes, whereas reimbursement is sought for at least 17 adult cancer indications (cancer types, including subtypes, represented in the clinical trial data) and potentially more cancer subtypes in which *NTRK* fusion mutation is present, but for which there is no clinical or health economic evidence. For all stratified analyses presented, the sponsor assumed the PFS and OS of the entrectinib arm were the same, regardless of tumour site, without clinical justification and in contradiction to the heterogeneity reported in the response rate and duration of response outlined within the CADTH clinical report. • The costs of identifying patients with *NTRK* fusion mutations are underestimated. The sponsor assumed that patients would largely be identified using IHC; however, CADTH clinical experts described IHC for detection of *NTRK* fusion mutations as still under development and not clinically validated with a known test accuracy for all tumour types. Clinical experts also indicated a strong preference for NGS testing because it can screen for multiple mutations at once without destroying the patient's pathology sample. • The sponsor's analysis extrapolated PFS and OS survival curves without assuming any treatment waning and, as such, under-representing the uncertainty of predicted long-term outcomes substantially past the observation period for specific tumour types. • The sponsor excluded any subsequent therapy costs for those who fail on a first-line therapy. If entrectinib was to be used in a first-line setting, the treatments it replaces would likely be used if the patient were to progress on entrectinib. The sponsor also excluded relevant health care costs that would be incurred by the patient over their lifetime. • CADTH identified numerous errors in the sponsor's model, such as using the height of an individual to determine dose rather than weight.
CADTH reanalysis results	• The CADTH reanalysis included the following changes: corrected costing errors; used tumour-specific PFS and OS data; applied different extrapolation methods to OS and PFS; applied relevant testing costs; considered a greater number of relevant tumour types; presented results for each tumour type; and included a scenario analysis comparing entrectinib to first-line therapies with and without subsequent therapy costs. • For the pooled analysis for second-line therapies: ◦ The ICER of entrectinib compared with BSC, averaged across all tumour sites, in patients known to have *NTRK* fusion cancers is $1,272,991 per QALY gained. ◦ No level of price reduction for entrectinib will achieve an ICER of $50,000 per QALY on the average cost-effectiveness across all indications. ◦ Incorporating the costs of case finding using NGS testing, the ICER of entrectinib compared with BSC care increases to $16,746,589 per QALY gained. There is no price reduction for entrectinib that will achieve an ICER of $50,000 per QALY. • CADTH notes there is a substantial amount of heterogeneity in the cost-effectiveness of entrectinib across individual tumour sites, with the ICER varying from $94,645 per QALY gained for MASC compared with sunitinib to higher costs but fewer QALYs for entrectinib compared with relevant comparators in various tumour sites (thyroid and CRC). • As a scenario analysis, CADTH analyzed the pooled analysis for comparators the sponsor identified as first-line therapies: ◦ The ICER of entrectinib compared with BSC, averaged across all tumour sites, in patients known to have *NTRK* fusion cancers is $2,057,174 per QALY gained. ◦ A price reduction of 82% for entrectinib may achieve an ICER of $50,000 per QALY on the average cost-effectiveness across all indications. However, this assumes patients on entrectinib would receive no subsequent lines of therapies. If subsequent therapy costs are incorporated, there may be no price

Component	Description
	reduction for entrectinib that will achieve an ICER of $50,000 per QALY. ◦ Incorporating the costs of case finding using NGS testing, the ICER of entrectinib compared with BSC care increases to $9,209,215 per QALY gained. There is no price reduction for entrectinib that will achieve an ICER of $50,000 per QALY.

BSC = best supportive care; CRC = colorectal cancer; ICER = incremental cost-effectiveness ratio; IHC = immunohistochemistry; MASC = mammary analogue secretory carcinoma; MSI-H = microsatellite instability-high; NGS = next-generation sequencing; NSCLC = non–small cell lung cancer; NTRK = neurotrophic tyrosine receptor kinase; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

Budget Impact

Based on a CADTH reanalysis, the estimated budgetary impact of funding entrectinib, assuming no displacement of other treatment options, is expected to be $69,746,533 in year 1, $42,266,837 in year 2, and $42,005,060 in year 3, for a 3-year budget impact of $154,018,431 when testing costs are included. When including only drug costs, the budgetary impact of reimbursing entrectinib is expected to be $13,444,089 in year 1, $9,080,920 in year 2, and $8,435,525 in year 3, for a 3-year budget impact of $30,960,534. CADTH was unable to account for the potential displacement of alternate therapies or for the potential funding of larotrectinib. Should larotrectinib be funded before entrectinib, the budgetary impact of reimbursing entrectinib would be substantially reduced in terms of both incremental drug and *NTRK* fusion–testing costs.

pERC Information

Members of the Committee

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. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

Meeting date: September 14, 2022

Regrets: None

Conflicts of interest: None