pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Larotrectinib (Vitrakvi)

Submitted Reimbursement Request: For the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion. Additional criteria: Age ≥ 1 month; ECOG score of ≤ 3; Tumour harbouring NTRK1, NTRK2 or NTRK3 gene fusion confirmed by a validated diagnostic testing method; Patients eligible for larotrectinib should have no satisfactory alternative treatments or have progressed following treatment.

Submitted By: Bayer Inc.	**Manufactured By:** Bayer Inc.
NOC/c Date: July 10, 2019	**Submission Date:** February 25, 2019
Initial Recommendation: August 29, 2019	**Final Recommendation:** October 31, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Larotrectinib costs $5,988.89 per bottle for a bottle of 56 capsules (25 mg strength) capsules; $17,966.67 for a bottle of 56 capsules (100mg strength); $8,555.56 per 100 mL oral solution (20 mg/mL). In adults and at the recommended dose of 100 mg twice per day, larotrectinib costs $641.67 per day (using 2 x 100 mg capsule) or $855.56 per day (using 8 x 25 mg capsule). In children and at the recommended dose of 100 mg/m^2 up to a maximum of 100 mg twice daily, i.e., maximum 200 mg daily, larotrectinib costs a maximum of $855.56 per day. In both adults and pediatric patients, larotrectinib may cost from $17,966.76 to $23,955.57 per 28-day cycle depending on the formulation used.

pERC RECOMMENDATION

☐ **Reimburse**

☐ **Reimburse with clinical criteria and/or conditions**[a]

☒ **Do not reimburse**

[a] If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement

pERC does not recommend the reimbursement of larotrectinib for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a neurotrophic tyrosine receptor kinase (NTRK) gene fusion.

pERC made this recommendation because the Committee was uncertain that there is a net clinical benefit of larotrectinib treatment compared with available treatment options or best supportive care. While pERC noted that larotrectinib treatment appears to be associated with anti-tumour activity, the Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit of larotrectinib given the heterogeneity of the patients in the included trials and pooled analysis, inability to interpret variation in outcomes by tumour type, lack of evidence as to whether or not the NTRK gene fusion is an oncogenic driver in all tumour types, and lack of historical evidence on outcomes with available therapies in patients with the gene fusion. pERC noted that the evidence available for outcomes important to decision-making, such as overall survival (OS) and progression-free survival (PFS), were uninterpretable given the heterogeneity of the tumours among

request.	the included patient population. pERC concluded that larotrectinib aligned with patient values based on its anti-tumour activity, manageable toxicity profile, and ease of administration as an oral therapy. The Committee could not draw any definitive conclusions regarding the cost-effectiveness of larotrectinib compared with available drugs given the heterogeneity of the patients included in the pooled analysis, which created considerable uncertainty in the magnitude of clinical benefit.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Reimbursement** pERC acknowledged that the SCOUT and NAVIGATE trials are currently ongoing with estimated primary completion dates in 2022 and 2023, respectively. pERC encouraged the provision of updated or additional evidence from sources that may include these or other clinical trials, as well as real-world evidence, to inform a resubmission.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

NTRK gene fusions are observed in variable frequencies across a spectrum of pediatric and adult solid tumours. There is some uncertainty regarding exact frequencies of the gene fusion across tumour types with estimates for incidence ranging from 0.1 to 1% in more commonly occurring cancers like non-small cell lung cancer (NSCLC) to 100% in less frequently occurring cancers like mammary analogue secretory carcinoma of the salivary gland. Generally, the NTRK gene fusion does not co-exist with other oncogenic driver mutations. Given the lack of data assessing the prognostic relevance of the NTRK gene fusion across cancer types, pERC had difficulty determining the burden of illness and need for treatment specifically targeting patients with the NTRK gene fusion. pERC further agreed that robust evidence is required to fully establish the role of the NTRK gene fusion in cancer prognosis. pERC acknowledged that among patients with tumour types that have no other known resistance mutation and have a high frequency of the NTRK gene fusion, who are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory treatment options, there is more certainty about the burden of illness and the need for new and effective treatment options. After weighing these factors, and with the absence of evidence confirming or refuting the tumour agnostic effect or prognostic effect of the NTRK gene fusion, pERC agreed that there is a need for new and effective treatment options in such patient populations.

pERC deliberated on the results of a pooled analysis from the LOXO-TRK-14001, SCOUT, and NAVIGATE trials, which evaluated larotrectinib in adult and pediatric patients with advanced or metastatic solid tumours. The primary outcome in the pooled analysis reported a high overall response rate (ORR) of 81% with the median duration of response (DOR) not being reached as of the latest data cut. PFS was 28.3 months at the latest data cut while OS, only available for an earlier data cut, was not mature. During deliberation on the Initial Recommendation pERC had agreed that, despite the various limitations in design of the three trials informing the pooled analysis, the pooled ORR results are large and impressive while the OS and PFS results are difficult to interpret given the methodological limitations of pooling patient populations with varying survival distributions. pERC agreed that the health-related quality of life (HRQoL) improvements reported are difficult to interpret given the exploratory nature of the analysis. Finally, pERC agreed that the low incidence of adverse events demonstrated that larotrectinib is well tolerated by patients. At that time, pERC agreed on the difficulty in coming to a conclusion regarding net clinical benefit within a setting that lacked evidence supporting or refuting the ability of the NTRK gene fusion status to predict clinical response to larotrectinib across tumour types, lacked historical evidence on outcomes in patients with the gene fusion, had various limitations in trial design (including and not limited to heterogeneous patient populations in the pooled analysis), and lacked of evidence supporting the surrogacy of ORR for PFS and/or OS. Given these uncertainties, pERC attempted to identify patients for whom larotrectinib might offer a more certain benefit and identified those who have no other known resistance mutation and have a high frequency of the NTRK gene fusion, who are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options. These criteria applied specifically to adult or pediatric patients with soft tissue sarcoma, adult or pediatric patients with salivary gland tumours, and pediatric patients with cellular congenital mesoblastic nephroma and infantile fibrosarcoma. Among all other patient populations, pERC agreed that the limitations associated with the trials and pooled analysis that had had an impact on the interpretability of the results as well as the uncertainty as to whether or not the NTRK gene fusion is an oncogenic driver made it difficult to conclude that there was a net clinical benefit across all tumour types harbouring an NTRK gene fusion. Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback from the sponsor, registered clinicians, patient advocacy groups, and the pCODR Clinical Guidance Panel (CGP) on the interpretation of the available evidence. Based on this feedback, pERC re-considered the robustness of the data presented in the pooled analysis and the evidence supporting the tumour agnostic effect of the NTRK gene fusion among patients harbouring the NTRK gene fusion. There were substantive re-deliberations based on this feedback, which is subsequently summarized.

In re-deliberating on the results of the pooled analysis, pERC considered feedback from stakeholders indicating that the available evidence should be evaluated based on the presence of the NTRK gene fusion (tumour agnostic effect) and not by individual tumour types. Feedback indicated that this was the approach taken in the Health Canada market authorization. Stakeholders stressed that the design of basket trials does not support the assessment of subgroups of individual tumour types and that the available evidence is not sufficient to demonstrate a tumour agnostic effect. pERC considered this feedback and acknowledged that the tumour-specific subgroup analyses were indeed an exploratory post-hoc analyses. pERC further acknowledged that the subgroup analysis by tumour type was not intended to be interpreted inferentially (i.e., the subgroups were not intended to be used to make conclusions about efficacy across individual tumour types). Based on this feedback and re-deliberation of the available evidence, pERC agreed that the available evidence cannot support a decision on reimbursement based on individual tumour types. The Committee therefore re-evaluated the available evidence for the full population rather than by tumour type and considered whether larotrectinib should be reimbursed for all patients with solid tumours harbouring an NTRK gene fusion protein. pERC further reiterated that there is not yet any conclusive evidence in the literature or submitted by the sponsor to support or refute a tumour agnostic or prognostic effect with the NTRK gene fusion in human populations. Therefore, the Committee did not accept the rationale offered by stakeholders and the CGP that the high ORR observed in these early studies is sufficient to demonstrate a tumour agnostic effect and form the basis for a reimbursement decision across all patients with solid tumours harbouring the NTRK gene fusion. pERC noted that other driver mutations have been observed to have differing roles on cancer biology across different tumours in a plethora of studies; therefore, further evidence is required to more confidently understand the role of the NTRK gene fusion. Based on a robust discussion of the evidence in which various strong opinions were expressed, the majority of pERC members agreed that the available evidence from the pooled analysis is too uncertain to aid the Committee in concluding that there is a net clinical benefit of larotrectinib for all adult and pediatric patients with locally advanced or metastatic solid tumours harbouring the NTRK gene fusion.

In re-deliberating and making this decision, pERC recognizes that its decisions must be equitable, transparent, timely, and accountable to patients, health care funders, and the public to ensure that effective treatment options are considered for public funding. pERC further recognized the changing landscape of oncology with the advent of precision medicine, the associated difficulty in recruiting sufficient numbers of patients for randomized controlled trials in these settings, and that consideration must be given to alternative pathways for assessing effectiveness and safety. Conversely, pERC also recognized that, despite the changing data generation landscape in oncology, the evidence package provided to health technology assessment bodies must continue to support rigorous, consistent, and evidence-based decisions. pERC expressed disappointment in having deliberated on evidence that showed great promise but noted that the lack of contextual evidence made it challenging for the Committee to adequately interpret the results. pERC noted that evidence demonstrating the role of the NTRK gene fusion in cancer prognosis, historical or real-world evidence on outcomes in patients harbouring the NTRK gene fusion, and the use of alternate methodologies for assessing OS and PFS in basket trials would have helped the Committee interpret the available evidence. pERC further noted that regulatory approval was conditional pending the results of trials to verify its clinical benefit. Although the current data set may be reasonable to allow the regulator to provide access to a promising new treatment in tumours with a high unmet need (specifically, where patients have no suitable alternative treatment options), pERC agreed that the available data constitute an unacceptably high degree of uncertainty to support public reimbursement. pERC therefore encouraged the future provision of evidence that may better inform the previously mentioned concerns on the efficacy and safety of larotrectinib in patients with the NTRK gene fusion (e.g., more mature data from the ongoing SCOUT and NAVIGATE trials, which are part of the regulatory requirement of the conditional Health Canada approval) as part of a resubmission to CADTH.

pERC deliberated on input from patient advocacy groups and noted that patients value a targeted treatment that improves symptom control, has better disease control, allows for a better quality of life, and provides patients with ease of administration. Input from patient groups indicated that patients have variable experiences with disease and treatment options. Key symptoms identified by patient input varied from no symptoms to those having symptoms that significantly affect day-to-day life. The most difficult symptoms experienced by patients were fatigue, pain, incontinence, shortness of breath, headaches, dizziness, and swelling. Among patients who had experience with larotrectinib, all patients indicated that it offered clinically meaningful responses. All patients said improvements happened quickly — some symptoms resolving within days of starting larotrectinib. All patients said larotrectinib helped them maintain high quality of life (QoL) with disease related symptoms being significantly improved or managed

better than on previous therapies. Patients expressed that all side effects were tolerable and minor. During deliberation on the Initial Recommendation, pERC had agreed that larotrectinib aligned with patient values based on the impact of larotrectinib on symptom control, its ability to provide better disease control, manageable toxicity profile and ease of administration. Upon reconsideration of the pERC Initial Recommendation, pERC carefully considered feedback from patient advocacy groups and acknowledged the desire for patients to access new and promising therapies. In considering feedback from patient groups regarding equity of access, pERC reiterated that the Committee strives to make decisions that are equitable, transparent, timely, and accountable to patients, health care funders, and the public. pERC, however, stressed that the evidence package informing reimbursement decisions must allow the Committee to adjudicate rigorous, consistent, and evidence-based decisions. Given the considerable limitations in the available evidence, pERC's re-deliberation considered the totality of the pooled analysis. Having considered various factors, pERC concluded that the available evidence is not sufficient to conclude that there is a net clinical benefit of larotrectinib for all adult and pediatric patients with locally advanced or metastatic solid tumours harbouring the NTRK gene fusion. pERC reiterated its disappointment in having deliberated on evidence that showed great promise but lacked sufficient clinical contextual evidence to help the Committee adequately interpret the results.

pERC considered the clinical trial evidence with the information provided through patient input and feedback and struggled to reconcile the experiences of individual patients with the pooled clinical trial data. The Committee had a robust discussion on the alignment of larotrectinib with patient values and various opinions were expressed throughout the meeting. While pERC was unable to draw a conclusion on the comparative effect of larotrectinib, pERC acknowledged that larotrectinib's anti-tumour activity, manageable toxicity profile, and ease of administration aligned with patient values. pERC reiterated that its decision on clinical effectiveness must be informed by robust clinical evidence and encouraged the resubmission of the evidence package for larotrectinib once additional evidence is acquired.

pERC deliberated on the cost-effectiveness of larotrectinib compared with available drugs. During deliberation on the Initial Recommendation pERC had acknowledged the difficulties in determining the cost-effectiveness of larotrectinib across a heterogeneous group of tumours and focused its deliberations on the main factors that impact the incremental cost-utility ratio (ICUR). At the time, pERC had agreed that the OS and PFS results from pooling a heterogenous population of patients are difficult to interpret and that there is no evidence supporting the surrogacy of ORR for PFS and/or OS. Based on these considerations, pERC agreed that it is unclear if larotrectinib confers a survival benefit in patients with NTRK-positive solid tumours and agreed that there was considerable uncertainty in the magnitude of the survival benefit modelled within individual tumour types as demonstrated in the 95% confidence interval (incorporated by the Economic Guidance Panel [EGP]) around each tumour-specific survival curve. pERC had also noted that costs associated with testing and drug acquisition will have an impact on the ICUR depending on the incidence of the NTRK gene fusion. pERC had also acknowledged that models for adult and pediatric patients with salivary gland tumours, pediatric patients with infantile fibrosarcoma, and pediatric patients with congenital mesoblastic nephroma were not available while cost-effectiveness analyses were available for the adult and pediatric populations for soft tissue sarcoma (STS). Despite the absence of tumour-specific models for part of the population in pERC's Initial Recommendation and based on factors that most impact the ICUR, pERC had agreed at that time that larotrectinib for the treatment of adult and pediatric patients with salivary gland tumours, adult or pediatric patients with STS, and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma is not cost-effective at the submitted price and according to EGP re-analyses. Upon reconsideration of the Initial Recommendation, pERC considered feedback from stakeholders on the clinical effect of larotrectinib, feedback that subsequently had an impact on pERC's decision about the cost-effectiveness of larotrectinib. pERC agreed with stakeholders' feedback that stressed that the available evidence cannot support assessment by subgroups and that pERC's evaluation must be based on the presence of the NTRK gene fusion (tumour agnostic effect). Based on these re-deliberations, the majority of pERC members agreed that the evidence available through the pooled analysis is not sufficient to conclude that there is a net clinical benefit of larotrectinib for all adult and pediatric patients with locally advanced or metastatic solid tumours harbouring the NTRK gene fusion. In considering the cost-effectiveness of larotrectinib within the full population of patients included in the pooled analysis, pERC reiterated that the model results for the full pooled analysis violated a number of modelling and statistical assumptions that led the EGP to reject this analysis. pERC therefore reiterated its agreement with the EGP that a cost-effectiveness estimate derived through such modelling techniques is difficult to interpret. Based on this discussion, the Committee concluded that it could not draw a conclusion on the cost-effectiveness of larotrectinib compared with available drugs using the results of the pooled analysis.

pERC considered the feasibility of implementing a reimbursement recommendation for larotrectinib and discussed that the additional cost of testing and incidence rate of NTRK gene fusion could result in a potentially large budget impact. Based on the EGP's reanalysis, pERC noted that for tumours with low incidence of the NTRK gene fusion, the budget impact is lower and disproportionately spent on testing rather than treatment. Among tumours where the NTRK gene fusion is more common, the budget impact is greater and driven more by the cost of treatment (rather than by screening). pERC agreed that it would be ideal for jurisdictions to have the NTRK mutation testing (RNA-based NGS testing, incorporation of NTRK gene fusion to existing testing panels and/or immunohistochemistry followed by RNA-based testing) at the time of diagnosis to manage both the patient population and the budget impact of a reimbursement recommendation. pERC further agreed that the implementation of testing for the NTRK gene fusion will likely have a large budget impact, particularly in more commonly occurring cancers where the NTRK gene fusion frequency is low (e.g., STS population).

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from seven patient advocacy groups (Canadian Cancer Survivor Network [CCSN], Colorectal Cancer Canada [CCC], Lung Cancer Canada [LCC], Neuroblastoma Canada [NC], Ontario Parents Advocating for Children with Cancer [OPACC], Sarcoma Cancer Foundation Canada [SCFC], and Thyroid Cancer Canada [TCC"])
- input from registered clinicians (one single clinician, and four joint clinician inputs, comprising of 26 oncologists and one pharmacist from Colorectal Cancer Canada [CCC; 11 clinicians], the Pediatric Oncology Group of Ontario [POGO; five clinicians], LCC [seven clinicians], and Cancer Care Ontario [CCO; three clinicians and one pharmacist])
- input from pCODR's PAG.

Feedback on the pERC Initial Recommendation was also provided by:

- four patient advocacy groups (CCSN, CCC, LCC, and NC)
- five registered individual or clinician groups (POGO, LCC, CCC, and CCO breast and skin disease site groups)
- PAG
- the submitter (Bayer Inc.).

The pERC Initial Recommendation was to recommend reimbursement of larotrectinib (Vitrakvi) for the treatment of adult and pediatric patients with locally advanced solid tumours who have an NTRK gene fusion (this recommendation pertains only to adult and pediatric patients with salivary gland tumours, adult or pediatric patients with STS, and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma), without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory treatment options.

Feedback on the pERC Initial Recommendation indicated that the manufacturer and two patient advocacy groups did not agree with the Initial Recommendation; two patient advocacy groups and four registered clinician groups agreed in part with the Initial Recommendation; and one registered clinician group and PAG agreed fully with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of larotrectinib (Vitrakvi) in the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a NTRK gene fusion.

Health Canada has issued marketing authorization for the use of larotrectinib for the treatment of adult and pediatric patients with solid tumours that have a NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory treatment options. The marketing authorization was issued with conditions, pending the results of trials to verify its clinical benefit. pERC agreed that any additional evidence that may be collected through the fulfillment of this regulatory requirement should be made available to jurisdictions and CADTH-pCODR to better inform the true effectiveness and cost-effectiveness of larotrectinib.

Studies included: Pooled analysis of select patients from three separate non-randomized trials with different designs

The pCODR systematic review was based on a pooled analysis of three, open-label, single-arm trials of larotrectinib (LOXO-TRK-14001, a phase I adult dose escalation and expansion trial; SCOUT, a phase I/II pediatric trial; and NAVIGATE, a phase II basket trial in adults and adolescents) in adult and pediatric patients with advanced or metastatic solid tumours.

The pCODR review also provided contextual information on two topics.

- Prognostic relevance of the NTRK gene fusion in patients with solid tumours: A literature search was conducted and did not identify any relevant information that addressed the prognostic relevance of the NTRK gene fusion across tumour types.
- Testing for Neurotrophic Receptor Tyrosine Kinase Gene Fusion.

Patient populations: Heterogeneous patient population across three trials informing the pooled analysis

Key eligibility criteria of the three trials included:

- LOXO-TRK-14001: adult patients (≥ 18 years of age), with ECOG performance score of 0 to 2, and locally advanced or metastatic solid tumours that had progressed, were nonresponsive to available therapies, were unfit for standard chemotherapy, or for which no standard or available curative therapy existed. NTRK gene fusion status was not among the inclusion criteria. In the dose escalation phase, patients received increasing dose levels of larotrectinib (50 mg daily to 200 mg twice daily) until the dose-limiting toxicity in cycle 1, or until the maximum tolerated dose was reached. Patients in the expansion cohorts were treated at the maximum tolerated dose, or at a dose level deemed by the sponsor to provide significant TRK inhibition. The primary end point of the study was the safety of larotrectinib (including dose-limiting toxicity) and identification of the maximum tolerated dose. Secondary end points included ORR and DOR. A total of 72 patients were enrolled into the trial. Patient enrolment is complete.
- LOXO-TRK-15003 (SCOUT): pediatric patients (infants, children, and adolescents one month old to 21 years old) with locally advanced or metastatic solid tumours or central nervous system (CNS) tumours that had relapsed, progressed, or had inadequate response to available therapies. Patients were required to have a Karnofsky (for patients aged ≥ 16 years) or Lansky (for patients aged <16 years) performance score of at least 50. There was no requirement for NTRK fusion gene for this study, but most patients entered were positive. Larotrectinib was administered in increasing doses in the phase I dose escalation phase (based on age and body surface area (BSA) in two cohorts and using a BSA-based dose for three additional cohorts). A starting dose of 100 mg twice daily was used in the phase I expansion and phase II trial based on previous testing in adults. Larotrectinib was administered orally twice daily, based on 28-day cycles. The primary end point of the phase I dose escalation component was the safety of larotrectinib, including dose-limiting toxicity. ORR (per RECIST version 1.1), PFS, OS, and assessment of pain and HRQoL were conducted in the phase I expansion and phase II stage of the trial. A total of 37 patients were recruited on the trial. Patient enrolment is ongoing.
- LOXO-TRK-15002 (NAVIGATE): nine cohorts of adolescent and adult patients with solid tumours harbouring NTRK fusions (NSCLC, thyroid cancer, sarcoma, colorectal cancer, salivary gland cancer, biliary cancer, primary CNS tumour, all other solid tumour types with evaluable but not measurable disease; and patients with an NTRK gene fusion identified in a lab where certification of the lab cannot be confirmed by the sponsor - all the testing was performed in a Clinical Laboratory Improvement Amendments–certified (or equivalent) laboratory). Patients were required to have an ECOG PS ≤ 3, or Karnofsky performance score of at least 50 for patients with CNS tumours. Larotrectinib was administered at 100 mg orally twice daily in patients with a BSA ≥ 1 m^2, or 100 mg/m^2 orally twice daily for children and adolescents with a BSA < 1 m^2, up to a maximum of 100 mg twice daily based on 28-day cycles. The primary end point of the trial was ORR, as determined by an independent radiology review committee using RECIST (version 1.1) or RANO criteria. Secondary end points included: investigator-assessed ORR, DOR, PFS, OS, and safety. HRQoL was measured as an exploratory end point. A total of 75 patients were recruited on the trial. Patient enrolment is ongoing.

In all three trials, treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal.

The pooled analyses included adult and pediatric patients who were enrolled across the three larotrectinib studies if they met the following criteria: documented NTRK gene fusion as determined by local testing; non–CNS primary tumour with one or more measurable lesions at baseline that could be assessed according to RECIST, version 1.1; and received one or more doses of larotrectinib. A total of 122 adult and pediatric patients with NTRK gene fusion cancer were included in the efficacy analysis population with an additional 70 patients included for the safety analysis. Patient ages ranged from 1.2 months to 80 years, with a median of 41 years. The majority of patients had an ECOG performance score of 0 or 1; and 45% of patients had received two or more prior systemic anti-cancer therapies. A total of 15

different tumour types were included with sample sizes ranging from n = 28 (adult STS) to n = 1 (appendix, CMN, pancreas and unknown primary site of tumour).

Key efficacy results: Inability to interpret PFS and OS results

The key efficacy outcome deliberated on by pERC included ORR, which was the primary end point of the pooled analysis. As of the 30-July-2018 data cut-off date, ORR was 81% (95% CI, 72% to 88%) in the pooled analysis; with 17% of patients achieving a complete response and 63% achieving a partial response. The median time to response was 1.8 months. At the data cut-off, 84% of responding patients (73% of all patients) remained on treatment or had undergone surgery with curative intent. The ORR results varied across the subgroups by tumour types, and NTRK gene fusion or major NTRK isoforms. ORR was however consistent across other subgroups based on baseline disease characteristics (ECOG status and metastatic cancer status) and number of prior treatment regimens. pERC agreed that the ORR results are large and impressive. Although acknowledging the challenges of interpreting subgroup results with very few patient numbers, pERC noted that the high ORR rates were variable when considering ORR by tumour type, with a 0% ORR in some tumours with only one patient in the tumour subtype. Upon reconsideration of the Initial Recommendation, pERC noted various feedback from stakeholders indicating that the evidence should be evaluated based on the presence of the NTRK gene fusion (tumour agnostic effect) and not by individual tumour types. pERC considered this feedback and acknowledged that the tumour-specific subgroup analyses were indeed exploratory post-hoc analyses. pERC further acknowledged that the subgroup analysis by tumour type was not intended to be interpreted inferentially (i.e., the subgroups were not intended to be used to make conclusions about efficacy across individual tumour types).

Key secondary endpoints in the pooled analysis included PFS and OS. At the 30-July-2018 data cut-off date, after a median follow-up of 19.6 months, the median PFS was 28.3 months (95% CI, 9.9 to not estimable). The submitter acknowledged that this estimate was "not statistically stable due to a low number of progression events, as evidenced by the wide confidence interval." OS results were only available for an earlier analysis performed at the 19-February-2018 data cut-off (extended primary data set; n = 73), where 86% of patients were still alive and 14% had died. After a median follow-up of 14.8 months, the median OS had not been reached. At 12 months, the probability of survival was estimated to be 90%. pERC agreed that the OS and PFS results are difficult to interpret given the methodological limitations of pooling patient populations with varying survival distributions.

Patient-reported outcomes: Difficult to interpret improvements given exploratory assessment

HRQoL and health utilities were exploratory end points in the NAVIGATE and SCOUT trials while these were not measured in the LOXO-TRK 14001 trial. The evidence on HRQoL was also noncomparative, open-label, and only collected in 57 of 122 patients. The minimally importance difference was defined as a change in score of ≥ 10 points for EORTC QLQ-C30, ≥ 4.5 points for PedsQL-Core score, and ≥ 10 points for the EQ-5D-5L visual analogue scale (VAS).

Of the 40 adult patients who completed two subsequent EORTC QLQ-C30 questionnaires, 70% had an improvement in global health scores, with 60% reporting improvements that reached or exceeded the minimally important difference of 10 points. Among evaluable patients, 41% had an improvement in EORTC QLQ-C30 global health score that lasted for at least two consecutive cycles. EORTC QLQ-C30 global health score improvements were reported for all tumour types. Within the EQ-5D measure, 73% had an improvement in VAS health score, with 60% reporting a post-baseline score that reached or exceeded the MID of 10 points. Among evaluable patients, 51% had an improvement in VAS health score that lasted for at least two consecutive cycles.

Of the 17 pediatric patients who completed two consecutive PedsQL-Core questionnaire, 88% had improvement in PedsQL total scores, with 76% reporting a best post-baseline score that reached or exceeded the MID of 4.5 points. Among evaluable patients, 65% reported improvements that lasted for at least two consecutive cycles. PedsQL total score improvements were observed across tumour types.

pERC considered the HRQoL data collected and agreed that the improvements reported are difficult to interpret given the exploratory nature of the analysis. pERC acknowledged that there is additional difficulty in interpreting HRQoL improvements in pediatric patients which range in age from ≥ two years to < 18 years.

Limitations: Extensive limitation in interpretability of available evidence

pERC considered the extensive limitations associated with the evidence base supporting the use of larotrectinib in adult and pediatric patients harbouring an NTRK gene fusion. pERC first noted a lack of historical evidence to determine prognostic impact of the gene fusion. pERC acknowledged that the NTRK gene fusions are rare and the natural history of the disease has not been well characterized to date. An independent search conducted by the CADTH-pCODR review team and confirmation from the submitter noted that there is no literature available that demonstrated the impact of NTRK gene fusion on patients' outcomes across tumour types. pERC also noted a lack of data on comparative efficacy and safety among cancers for which there are established standards of care (e.g., targeted therapies or immunotherapies). Upon reconsideration of the Initial Recommendation, pERC noted feedback from the sponsor regarding additional literature addressing the prognostic ability of the NTRK gene fusion. With the exception of one study, all cited studies were conducted in mouse models or cell cultures. Overall, none of the studies identified provide further evidence on the role of the NTRK gene fusion in disease prognosis.

Secondly, pERC considered heterogeneity in the design of the trials used to inform patients included in the pooled analysis. These included different phases of studies combined (a phase I adult trial [LOXO-TRK 14001], a phase I/II pediatric trial [SCOUT], and a phase II basket trial [NAVIGATE] in adults and adolescents); different primary outcomes across trials (safety and tolerability of larotrectinib as a primary objective in the LOXO-TRK 14001 and SCOUT studies, while the primary objective of the NAVIGATE trial was efficacy of larotrectinib based on best ORR); different requirements for outcome measurement where assessment of ORR was based on investigators in the LOXO-TRK 14001 and SCOUT trials while an independent committee assessed ORR in the NAVIGATE trial; and differences in eligibility criteria where the presence of a confirmed NTRK gene fusion was mandated before enrolment in the NAVIGATE trial; while NTRK-positive status was not a requirement in the LOXO-TRK 14001 and SCOUT trials with prospective confirmation of TRK gene fusions in the two latter trials. pERC agreed that the between-study heterogeneity creates considerable difficulty in pooling results across the three trials.

Finally, pERC noted that pooling data across tumour types may lead to false-positive results as the treatment effect could be heterogenous across tumour types. pERC discussed that analysis of the data by subgroups from the three trials (integrated analysis; n = 122) indicated that ORR results varied across tumour types. The reported ORR benefit ranged from 100% in thyroid cancer, gastrointestinal stromal tumour (GIST) and CMN to 0% in appendix, pancreas and breast cancers, and cholangiocarcinoma. Furthermore, 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 of all study patients. Given this, there is considerable difficulty in interpreting results which pool data on survival outcomes (i.e., PFS and OS) across different tumour types.

Overall, pERC had a fulsome discussion in determining how meaningful the results of the pooled analysis was across all patients within the pooled analysis and the broader population of patients with the NTRK gene fusion. pERC agreed that further evidence is required to confirm the efficacy and safety of larotrectinib in the broader population and further evidence is needed to address the predictive and prognostic impact of the NTRK gene fusion. Based on this, the Committee was unable to generalize the overall trial results across all patients with an NTRK gene fusion. During deliberation on the Initial Recommendation, pERC had identified patients who have tumours with no other known resistance mutations and harbour a high frequency of the NTRK gene fusion, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory treatment options among the population of patients who may have more certainty of clinical benefit with larotrectinib treatment. pERC had further acknowledged the promising results in all other tumour types included in the pooled analysis. However, pERC agreed that the limitations associated with the trial which had an impact on the interpretability of the results and the uncertainty as to whether or not the NTRK gene fusion is an oncogenic driver, could not be overcome. Therefore, the Committee could not conclude that there was a net clinical benefit across all tumour types harbouring an NTRK gene fusion.

Upon reconsideration of the Initial Recommendation, pERC noted feedback from stakeholders indicating that the pERC reimbursement population should be aligned with the Health Canada market authorization population and that the evidence should be evaluated based on the presence of the NTRK gene fusion (tumour agnostic effect) and not by individual tumour types. pERC considered this feedback and acknowledged that the tumour-specific subgroup analyses were indeed an exploratory post-hoc analyses. pERC further acknowledged that the subgroup analysis by tumour type was not intended to be interpreted inferentially (i.e., the subgroups were not intended to be used to make conclusions about efficacy across

individual tumour types). The Committee therefore re-evaluated the available evidence as a whole and considered whether or not larotrectinib should be reimbursed in all adult and pediatric patients with solid tumours harbouring an NTRK gene fusion protein. pERC further reiterated that there is not yet any conclusive evidence in the literature or submitted by the sponsor to support or refute a tumour agnostic effect or prognostic effect with the NTRK gene fusion. Therefore, the Committee did not accept the rationale by stakeholders and the CGP that the high ORR observed in these early studies is sufficient to demonstrate a tumour agnostic effect leading to a reimbursement decision across all patients with solid tumours harbouring the NTRK gene fusion. pERC noted that other driver mutations have been observed to have differing roles on cancer biology across different tumours in a plethora of studies; therefore, further evidence is required to more confidently understand the role of the NTRK gene fusion. Based on a robust discussion of the evidence in which various strong opinions were expressed, the majority of pERC members agreed that the available evidence from the pooled analysis is too uncertain to aid the Committee in concluding that there is a net clinical benefit of larotrectinib for all adult and pediatric patients with locally advanced or metastatic solid tumours harbouring the NTRK gene fusion.

Safety: Low incidence of toxicity, well tolerated

pERC discussed the toxicity profile of larotrectinib. Among the 207 patients included in the safety analysis data set, the majority of the reported adverse events (AEs) were grade 1 or 2. Treatment-related Grade 3 or 4 AEs occurred in less than 5% of patients. The most common Grade 3 or 4 AEs included anemia, increase in liver enzyme (alanine transaminase, ALT and aspartate transaminase, AST) levels, and nausea. Eleven out of the 122 patients (9%) in the integrated analysis set required dose reductions due to AEs, and all patients maintained tumour regression on a reduced dose. Two patients discontinued larotrectinib due to an AE. pERC deliberated on the toxicity profile of larotrectinib and agreed that the low incidence of AEs demonstrated that larotrectinib is well tolerated by patients.

Need and burden of illness: Uncertainty in the burden of illness and need for treatments targeting the NTRK gene fusion

NTRK gene fusions are observed in variable frequencies across a spectrum of pediatric and adult cancers. There is some uncertainty regarding exact frequencies of the NTRK gene fusion in tumours with estimates for incidence ranging from 0.1 to 1% in more commonly occurring cancers like NSCLC to 100% in less frequently occurring cancers like mammary analogue secretory carcinoma of the salivary gland. Generally, the NTRK gene fusion does not co-exist with other driver mutations, with small studies reporting co-localization with PD-L1 gene alteration, EGFR and MET amplification and others in a smaller proportion of patients. pERC discussed the absence of literature assessing the prognostic relevance of the NTRK gene fusion in cancer and the absence of evidence demonstrating historical outcomes of patients harbouring the NTRK gene fusion. During deliberation on the Initial Recommendation pERC had agreed that, until more robust evidence is made available, reimbursement of larotrectinib should be for specific tumour types based on the balance of clinical considerations focused on need for treatment options. pERC had acknowledged that among select patients who have no other known resistance mutation and harbour a high frequency of the NTRK gene fusion, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory treatment option, there may be more certainty of the burden of illness and need for new and effective treatment options that target a known mutation (NTRK gene fusion in this instance). On the balance of these factors, and in the absence of evidence confirming or refuting the tumour agnostic or prognostic effect of the NTRK gene fusion, pERC agreed that there is a need for new and effective treatment options in such patient populations.

Registered clinician input: Sequencing and need of larotrectinib dependent on tumour type; need for more evidence in some tumour types, testing an important consideration

Input was received from one single clinician and four joint clinician inputs comprising 26 oncologists and one pharmacist from the following groups: Colorectal Cancer Canada (CCC; 11 clinicians), the POGO; (five clinicians), LCC; (seven clinicians), and CCO; (three clinicians and one pharmacist).

Clinicians noted that a variety of drugs are currently used in patients with NTRK-positive solid tumours, including conventional cytotoxic drugs in subsets of pediatric malignancies harbouring the NTRK gene fusion, and chemotherapy and immunotherapy in lung cancer. Some of these therapies were stated to have fewer side effects and lead to better QoL compared with cytotoxic chemotherapy (e.g., immunotherapies). Clinicians also noted that large randomized controlled trials with patients harbouring the NTRK gene fusion are unlikely to be conducted. CCO clinicians stated that a phase I study with one breast cancer patient is insufficient evidence to extrapolate the use of larotrectinib to breast cancer

patients. CCO therefore agreed that there is no unmet need for larotrectinib in patients with breast cancer.

While acknowledging the limited data available, clinicians identified that for patients with colorectal, pancreas or cholangiocarcinoma, larotrectinib offers a significant improvement beyond current standard options based on its route of administration and lack of chemotherapy-related toxicity. For other settings including GIST and hepatocellular carcinoma, larotrectinib would be an additional treatment option along with available standard drugs (sunitinib, imatinib and regorafenib in GIST and sorafenib and regorafenib in HCC). A number of groups including LCC, POGO and the single clinician input highlighted the benefit of larotrectinib as related to its safety profile. Tolerability and duration of disease control were stated to be remarkable across the board, showing superiority over cytotoxic chemotherapy regimens and immunotherapy, which can be associated with significant immune-mediated AEs.

Generally, clinicians noted that for patients in whom the NTRK gene fusion occurs with high frequency and for whom upfront therapy of choice remains surgical resection and includes potential for significant morbidity (infantile fibrosarcoma, cellular CMN, secretory breast cancer and mammary analogue secretory carcinoma of the salivary gland [MASC]), patients should be considered candidates for larotrectinib if low intensity/low toxicity cytotoxic therapy (such as vincristine and dactinomycin) are insufficient to control disease and allow resection. Clinicians further noted that larotrectinib should be prioritized over traditional cytotoxic drugs with higher potential late effects such as anthracyclines or alkylators. For patients where the NTRK gene fusion occurs with low frequency, clinicians' decision on treatment with larotrectinib varied by disease prognosis. For patients in whom prognosis is poor (i.e., high-grade gliomas, metastatic sarcoma, metastatic papillary thyroid cancer), larotrectinib therapy should be considered as part of front-line therapy. For patients in whom prognosis is good, clinicians noted that larotrectinib be reserved as a second-line therapy until evidence showing equivalent or better than current front-line therapy is available.

There was no consensus from input received by clinicians on the sequencing of larotrectinib compared with currently available drugs. Generally, clinicians prefer to use larotrectinib in front-line therapy for pediatric populations. Among gastrointestinal solid tumours (colorectal, pancreatic, hepatocellular carcinoma and cholangiocarcinoma), clinicians indicated a preference to use larotrectinib first-line and beyond.

All clinicians agreed that patients eligible for larotrectinib would need to present with solid tumours harbouring the NTRK gene fusion. Clinicians further noted that there is no routine testing for the NTRK gene fusion currently available, and that testing is not funded, although it is anticipated that availability of NTRK testing will increase over the next five years given the increasing number of targeted therapies, and the declining cost of NGS testing. A variety of tests to identify the NTRK gene fusion were stated. A number of clinician groups noted that testing for the NTRK gene fusion is likely to be added to existing NGS panels (e.g., colorectal cancer, lung cancer). Ideally identification of the NTRK gene fusion would occur during diagnosis of the patient's tumour, or during testing for other mutations. However, there was no consensus on the timing of testing.

During deliberation on the Initial Recommendation, pERC had agreed that the reimbursement population should be limited to adult and pediatric patients with salivary gland tumours, adult or pediatric patients with STS and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma. pERC had also noted that this population for reimbursement of larotrectinib was in alignment with input from registered clinicians. pERC further supported the provision of additional evidence to help inform the efficacy and safety of larotrectinib in the broader population. Upon reconsideration of the Initial Recommendation, pERC discussed feedback from all stakeholders, including registered clinicians, and agreed that a decision on reimbursement cannot be made for individual tumour groups. Based on this, the Committee re-evaluated the available evidence as a whole and concluded that the available evidence from the pooled analysis cannot support a positive reimbursement recommendation for the use of larotrectinib in all patients with solid tumours harbouring the NTRK gene fusion protein.

pERC noted feedback relating to the need for new treatments targeting the NTRK gene fusion protein. pERC reiterated that the lack of information confirming or refuting the tumour agnostic effect of the NTRK gene fusion and lack of historical or real-world evidence on outcomes with current therapies made it difficult for the Committee to determine the need for a therapeutic option that targets the NTRK gene

fusion. pERC reiterated that other driver mutations have been observed to have differing roles on cancer biology across different tumours in a plethora of studies; therefore, further evidence is required to more confidently understand the role of the NTRK gene fusion in the current setting.

PATIENT-BASED VALUES

Values of patients with NTRK-positive solid tumours: Symptom control, disease control, better QoL, ease of administration

pERC deliberated upon collaborative input from seven patient groups, most of which were collected through US institutions or patients in the US with experience using larotrectinib. pERC noted that patients value a treatment that improves symptom control, has better disease control, allows for a better QoL, and provides patients with ease of administration. Input from patient groups indicated that patients have variable experiences with disease and treatment options. Key symptoms identified by patient input varied from no symptoms to those having symptoms that significantly affect day-to-day life. The most difficult symptoms experienced by patients were fatigue, pain, incontinence, shortness of breath, headaches, dizziness and swelling. Patient respondents reported that larotrectinib is a targeted drug that offered improvement in cancer symptoms, better disease control, manageable toxicities, ease of administration and maintenance of a high level of QoL.

The prognosis of cancer in some patients, especially in lung cancer, was described as feeling like a death sentence. Sarcoma patients experience an invasive and aggressive disease, affecting both children and young adults. Treatment with surgery for these patients can lead to loss of limbs and long rehabilitation.

All patients providing input had previous treatment with chemotherapy, surgery, radiation, immunotherapies, and/or targeted therapies. Patients indicated that they had exhausted other options. Patients with STS described having a struggle to find effective treatments. Chemotherapy in lung cancer and sarcoma patients was described to have many well-documented side effects ranging from minimal to debilitating effects including nausea, vomiting and extreme fatigue. Chemotherapy also requires multiple hospital visits for administration, treatments for toxicities and delayed adverse effects. Patients noted that immunotherapies have fewer side effects (or are better managed) and provide better QoL than chemotherapy. Lastly, patients acknowledged that targeted therapies have created a new paradigm for lung cancer patients. Some patients described going into debt to access treatments, including incurring the loss of homes, marriages, careers, experiencing depression, and reduced QoL.

Caregivers indicated that the illness and treatment limit QoL their and the patients' QoL. The poor prognosis and stigma of lung cancer leads to worry, isolation, anxiety and depression. Furthermore, the surgeries and rehabilitation for sarcoma affect marriages and career prospects of younger patients.

Patient values on treatment: better QoL, better survival, improved symptom control, ease of administration

Patients' expectations of the new treatment include better QoL while managing disease. Lung cancer patients expressed a desire for better survival rates, improved symptoms and an easier form of treatment, while sarcoma patients often experience quick disease progression and without long-term effective treatments, expressed a desire for reduction in pain, increase in mobility, and ease of breathing.

Among the 14 patients (one pediatric and 13 adults) who had experience with larotrectinib, all indicated that larotrectinib offered clinically meaningful responses to cancer (resolved completely, significantly or to a great extent) according to scans. The sarcoma patients (SCFC) were several years into their treatment and had not experienced any disease regression or reappearance of tumours. All patients also said improvements happened quickly — some symptoms resolving within days of starting larotrectinib. All said larotrectinib helped them maintain high QoL with disease-related symptoms being significantly improved or managed better than on previous therapies. Side effects experienced by patients while on larotrectinib included elevated ALT/AST levels, tinnitus, swollen ankles, withdrawal-like symptoms, overstimulation, fatigue, sensitivity to light, and flu-like symptoms. Patients expressed that all side effects were tolerable and minor. Despite the absence of robust clinical evidence to guide pERC's deliberation, the Committee commended the substantial collaborative work undertaken by patient groups, including extensive interviews, which helped pERC better understand the impact of treatment,

the quick onset of clinical effect, the nature of the side effects and the ways in which larotrectinib contrasts with other treatments.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis based on six tumour-specific models and one model pooling all patients

The EGP assessed the submitted cost-effectiveness and cost-utility analyses of larotrectinib for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring an NTRK gene fusion.

Seven separate analyses were included in the submitted base case. One model was based on the pooled analysis comparing larotrectinib with standard chemotherapy in individual settings, hereafter referred to as best supportive care (BSC) for each of the 14 tumour types included in the analysis from three clinical trials informing the efficacy and safety outcomes. Notably, the six other tumour-specific analysis were available assessing larotrectinib in subgroups of patients with colorectal cancer (CRC - comparators: trifluridine plus tipiracil; BSC); NSCLC - comparators: pembrolizumab plus platinum; nivolumab; BSC); melanoma (comparator: BSC); thyroid cancer (comparators: lenvatinib; BSC); adult STS (comparator: BSC); and pediatric STS (comparator: BSC).

Although requested by the EGP, the submitter was unable to provide a model for salivary gland tumours, despite this tumour type having the largest sample size in the clinical trials (n = 13). The submitter explained that there was insufficient information on the natural history of salivary gland tumours, a lack of reference data for other relevant inputs, and a lack of information on the selection of appropriate comparators in this setting to build a site-specific model. For all other cancers, the submitter further clarified that a consistent range of cost-effectiveness results was demonstrated and, given the limitations of the data, there is a diminishing value gained with additional models.

Basis of the economic model: Key costs underestimated, limited evidence informing survival curves for intervention arm

Key costs included were drug acquisition cost, diagnostic testing costs, non-treatment health care costs (surveillance and active follow-up for the “progression free and responsive to treatment,” “progression free, but not responding to treatment/stable disease,” and “progressed disease” states and terminal care) and cost of AEs. pERC noted that non-treatment health care costs, testing costs and likely AE costs were underestimated in the submitted models.

Key clinical effect estimates considered in the various analyses included OS, PFS, utilities, and disutilities associated with AEs. The efficacy and safety evidence for larotrectinib came from an integrated analysis of three studies (LOXO-TRK-14001, LOXO-TRK-15002 or NAVIGATE, LOXO-TRK-15003 or SCOUT). Kaplan-Meier data for PFS and OS were based on tumour-specific subgroup survival curves. pERC noted that uncertainty in tumour-specific larotrectinib survival curves was not captured in the probabilistic analysis for 15 cycles (trial data) and hence, in some situations 100% PFS and OS were assumed certain despite very small sample sizes and short follow-up period. This was modified in the EGP reanalysis. The efficacy and safety for the comparators (where available) came from representative studies selected by the submitter to characterize the range of potential outcomes associated with the comparators. The comparator arms were not composed of patients selected based on the NTRK gene fusion status. No formal quantitative indirect treatment comparison was performed.

Drug costs: High cost of treatment

In adults and at the recommended dose of 100 mg twice per day, larotrectinib costs $641.67 using 2 x 100 mg capsule or $855.56 using 8 x 25 mg capsule per day. In children and at the recommended dose of 100 mg/m^2 up to a maximum of 100 mg twice daily, i.e., maximum 200 mg daily, larotrectinib costs a maximum of $855.56 per day with the oral solution. In both adults and pediatric patients, larotrectinib may cost from $17,966.76 to $23,955.57 per 28-day cycle depending on the formulation used.

The following comparators were considered in the submitted economic evaluation. Costs are based on a 28-day cycle:

- CRC: Trifluridine/tipiracil ($6,219.96), BSC (5-fluorouracil-oxaliplatin-leucovorin, $4,693).

- NSCLC: Pembrolizumab plus Platinum ($11,733), Nivolumab ($8,213), BSC (docetaxel-pemetrexed-topotecan, $4,065).
- Melanoma: BSC (dacarbazine-temozolomide-carboplatin-paclitaxel, $2,721).
- Thyroid: Lenvatinib ($6,184), BSC (doxorubicin-cisplatin, $800).
- Adult STS: BSC (Doxorubicin plus ifosfamide, $1,039).
- Pediatric STS: BSC (Vincristine-dactinomycin-cyclophosphamide — VAC, $95).
- GIST: BSC (Imatinib-sunitinib, $4,465).
- Other sarcoma: BSC (doxorubicin, $933).
- MASC: BSC (Doxorubicin-5-fluorouracil-cisplatin-vinorelbine-oxaliplatin-carboplatin-paclitaxel-docetaxel-methotrexate-ifosfamide-gemcitabine, $1,342).
- Cholangiocarcinoma: BSC (gemcitabine-cisplatin-5-fluorouracil, $344).
- Breast: BSC (capecitabine-epirubicin-doxorubicin-fulvestrant, $1,589).
- Appendix: BSC (capecitabine-5-fluorouracil-irinotecan-raltitrexed-oxaliplatin-leucovorin-folinic acid, $3,225).
- Pancreatic: BSC (5-fluorouracil-gemcitabine, $181).

Clinical effect estimates: Considerable uncertainty in survival estimates and cost inputs

pERC deliberated on the cost-effectiveness of larotrectinib compared with available drugs. During the deliberations on the Initial recommendations, pERC had noted that among the seven models provided to evaluate the cost-effectiveness of larotrectinib, the model with the results of the full pooled analysis violated a number of modelling and statistical assumptions which caused the EGP to reject this analysis. These limitations included 1) "pooled" survival curves violate the Markov assumption of population homogeneity as the composition of patients in the pooled PFS and OS curves changes over time (patients with a tumour type with poor prognosis will leave the "at-risk" population earlier due to faster rates of progression or death); 2) Markov assumption of homogeneity of the population in a health state is also violated for costs and utilities aspect of the model as the submitter assumed constant costs and utilities associated with each health state despite dramatic changes in patient mix over time; 3) an "average" ICUR across multiple indications and patient populations with different comparators, across which the treatment may be differentially effective is difficult to interpret. Based on this, pERC had agreed with the EGP and based its decision on cost-effectiveness only on the results of the tumour-specific models. At that time, pERC noted that the evidence informing the available models (n = 4 in some instances), created considerable uncertainty in the submitted and EGP's reanalysis estimates. pERC further noted that the available tumour-specific models did not address all the specific patient populations included in the reimbursement population defined by the Committee. pERC also acknowledged the rationale provided by the submitter indicating that a consistent range of cost-effectiveness results were demonstrated across the seven models provided and, given the limitations of the data, there is an expectation that the value of insight to be gained with any additional site-specific models diminishes. Given the limitation of interpreting the pooled OS and PFS results and the lack of evidence supporting the surrogacy of ORR for PFS and/or OS, pERC agreed that it is unclear if larotrectinib confers a survival benefit in patients with NTRK-positive solid tumours. pERC had further agreed that there was considerable uncertainty in the magnitude of the survival benefit modelled within individual tumour types as demonstrated in the 95% confidence interval (incorporated by the EGP) around each tumour-specific survival curve. pERC had also noted that costs associated with testing or drug acquisition would have a big impact on the ICUR. pERC discussed that the cost of testing had a substantial impact on the ICUR particularly when the incidence of the NTRK gene fusion is low or when there was a low-cost comparator option. Despite the absence of tumour-specific models in all populations included in pERC's Initial Recommendation (salivary gland tumours, sarcoma and pediatric patients with infantile fibrosarcoma and CMN) and based on the factors that most impact the ICUR, pERC had agreed that larotrectinib for the treatment of adult and pediatric patients with salivary gland tumours, adult or pediatric patients with STS, and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma, is not cost-effective based on EGP re-analyses and at the submitted price.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from stakeholders on the clinical effect of larotrectinib, which subsequently had an impact on pERC's decision on the cost-effectiveness of larotrectinib. pERC agreed with stakeholders' feedback that stressed that the available evidence cannot support assessment by subgroups and that pERC's evaluation must be based on the presence of the NTRK gene fusion as a whole (tumour agnostic effect). Based on these re-deliberations, the majority of pERC members agreed that the evidence available through the pooled analysis is not sufficient to conclude that there is a net clinical benefit of larotrectinib for all adult and pediatric patients with locally advanced or metastatic solid tumours harbouring the NTRK gene fusion. In considering the cost-effectiveness of larotrectinib within the full population of patients included in the

pooled analysis, pERC reiterated that the model providing results of the full pooled analysis violated a number of modelling and statistical assumptions, which led the EGP to reject this analysis. pERC therefore reiterated its agreement with the EGP that an ICUR gain through such modelling technique is difficult to interpret. Based on this discussion, the Committee determined that it could not draw a conclusion on the cost-effectiveness of larotrectinib compared with available drugs using the results of the pooled analysis.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Potentially large budget impact due to testing implementation

pERC considered the feasibility of implementing a reimbursement recommendation for larotrectinib and noted that incorporation of testing costs for all cancer sites, duration of larotrectinib therapy, the frequency of testing, and the frequency of NTRK gene fusion had the largest effects impact on the budget impact analysis. Based on the EGP's reanalysis, pERC noted that for tumours with lower incidence of the NTRK gene fusion, the budget impact is lower and disproportionately spent on testing compared with treatment. Among tumours where the NTRK gene fusion is more common, the budget impact is greater and driven more by the price of treatment (rather than by screening). Upon reconsideration of the Initial Recommendation, pERC considered feedback from the sponsor on the estimated number of patients needing testing and costs associated with testing. pERC noted additional clarification from the EGP noting that accurate estimates of the number of patients to be tested and how the NTRK gene test would be rolled out is currently unclear. For the EGP analysis, the numbers of patients to be tested were based on clinical opinion and various methods of screening (e.g., immunohistochemistry only) were incorporated in the EGP analysis. Furthermore, costs related to testing are expected to vary by jurisdiction and may become less costly in the future. Cost estimates provided by the EGP, however, considered current costs.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Drs. Henry Conter, Avram Denburg, Christian Kollmannsberger, and Dominika Wranik who were not present for the meeting
- Valerie McDonald and Dr. Winson Cheung who were excluded from voting due to a conflict of interest.

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Maureen Trudeau and Dr. Kelvin Chan who were not present for the meeting
- Valerie McDonald and Dr. Winson Cheung who were excluded from voting due to a conflict of interest

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of larotrectinib (Vitrakvi) for NTRK solid tumours, through their declarations, one member had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, this member was excluded from voting.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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