CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Patient Advocacy Group)

Larotrectinib (Vitrakvi) for NTRK+ solid tumours

October 31, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Larotrectinib (Vitrakvi)
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Group):	Patient Group
Organization Providing Feedback	Colorectal Cancer Canada (CCC)

**The pCODR program may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by the pCODR program.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☐ agrees in part ☒ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the Initial Recommendation. If the Stakeholder agrees in part or disagrees with the Initial Recommendation, please provide specific text from the recommendation and rational. Please also highlight the applicable pERC deliberative quadrants for each point of disagreement. The points are to be numbered in order of significance.*

CCC respectfully disagrees with pERC's initial recommendation 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 for the following reasons:

1. It confuses the effectiveness of larotrectinib among patients with NTRK gene fusions with the frequency of NTRK gene fusions in different disease sites. Although this recommendation is appropriate for the included tumour types (all of which are very rare tumour types), it discriminates against individuals harbouring NTRK gene fusions in disease sites with lower frequencies, without substantial evidence to warrant this

decision. Indeed, as represented in the Clinical Guidance Report on page 31 section B, and in the illustrated CCC summary, patients in the excluded disease sites benefitted greatly from the drug and were better able to control their symptoms while taking larotrectinib (CGR, p. 31), which included groups of patients excluded in the initial recommendation.

2. Inconsistencies in the recommendation are highlighted by the fact that a positive funding recommendation was given for the treatment of locally advanced or metastatic cancers with NTRK gene fusions in disease sites with lower NTRK gene frequencies than others which were excluded from the recommendation. For example, the recommendation includes adult and pediatric patients with soft tissue sarcoma (STS), though the estimated frequency of NTRK gene fusions is 0.5% to 2.0% and the annual incidence of STS is 1,130 in Canada (the overall response rate of larotrectinib in patients with STS is 100%) (CGR, p. 73; 87). However, the recommendation excludes those, by way of example, with thyroid cancers, in which the estimated frequency of NTRK gene fusions is 1.5% to 12% and the incidence is 7,100 in Canada, despite an overall response rate of 100% (CGR, p. 14; 73; 87).

3. It is a missed opportunity for the development of real-world evidence based on a notice of compliance with conditions (NOC/c). Specifically, this recommendation deprives patients with locally advanced or metastatic disease who harbour the NTRK gene fusion and have exhausted all other available therapies of the opportunity to access a drug that is highly effective, is proven to improve quality of life, and results in minimal toxicities (Initial recommendation, p. 5; 31-40). Patients with the aforementioned criteria who are presently suffering from disease are not likely to survive during the interim period as they await a recommendation resulting from a resubmission to pERC in 2023, following the final results of SCOUT and NAVIGATE trials due to the fact that they are all in stages of advanced cancer and have exhausted all other treatment options (Initial recommendation, p.3).

4. While CCC acknowledges the high cost associated with testing for NTRK gene fusion, there is an opportunity for the manufacturer to relieve this cost – on an interim basis – in order to collect sufficient real-world data through patient support programs and other special access initiatives to provide a full recommendation for reimbursement in additional disease sites. By way of example, similar assistance was provided by the manufacturers of anti-EGFR drugs for KRAS testing.

5. As a result of this initial recommendation, there remains an unmet need for patients with locally advanced or metastatic disease harbouring NTRK gene fusions, particularly those who have exhausted all other therapeutic options. This decision is not to the overall benefit of society, given that the majority of NTRK-positive patients are excluded from accessing larotrectinib, many of whom would have accessed this drug after having exhausted (or been unsuitable for) all other available therapies (larotrectinib would have been utilized as a last-line therapy) (CGR, p. 50).

CCC strongly urges pERC to reconsider its initial recommendation, broadening access as a tumour agnostic, personalized medicine, based on the presence of NTRK gene fusions.

Personalized medicines are based on the presence of a biomarker, rather than the presence of mutations in a particular site.

CCC also recommends entering into a risk sharing agreement with the manufacturer for the purpose of sharing the costs associated with screening and the cost of the drug for those with locally advanced or metastatic solid tumours harbouring a NTRK gene fusion.

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☐ agrees ☐ agrees in part ☒ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the provisional algorithm. Please note that comments should relate* ***only to the proposed place in therapy of the drug under review*** *in the provisional algorithm. If feedback includes New Information or about other therapies that are included in the provisional algorithm, the information will not be considered and will be redacted from the posted feedback. Substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.*

CCC disagrees with the provisional algorithm for the reasons stated above.

c) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence or provisional algorithm) clearly worded? Is the intent clear? Are the reasons clear?

Please see comments provided in section 3.1 a).

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder wold support this Initial Recommendation proceeding to Final pERC Recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

☐ Support conversion to Final Recommendation.

Recommendation does not require reconsideration by pERC.

☒ Do not support conversion to Final Recommendation.

Recommendation should be reconsidered by pERC.

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Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
11	Overall Clinical Benefit	Para 1	"pERC acknowledged that among select patients who harbour a high frequency of the NTRK gene fusion, have no other known resistance mutation, 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 a burden of illness and need for new and effective treatment options that target a known mutation." This decision is inequitable, as it diminishes the experience and burden of disease among the majority of Canadians harbouring NTRK gene fusions. The presence, rather than the frequency of NTRK gene fusion, is relevant to this decision. Thus, the data upon which pERC has provided this initial recommendation are in fact highly generalizable.
13	Patient-Based Values	Para 2	"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." As personalized medicines are based upon the presence of a unique biomarker, to conclude that larotrectinib should be restricted to a few disease sites, despite being aligned with patient values (not to mention being highly effective) is unfounded. Further, the patient input upon which pERC has made this initial recommendation excludes many disease sites. The only tumour types named in the "Patient-Based Values" section are soft tissue sarcoma and lung cancer. It should be noted, however, that the input from

			lung cancer patients was ignored in this initial recommendation which does not pertain to individuals with lung cancer. This is also evidenced in the Clinical Guidance Report, in which, "CCSN reported that five patient respondents in the survey all reported having experience with larotrectinib. The five patient respondents taking larotrectinib all indicated a significant improvement in their symptoms and their overall outcomes as a result of taking larotrectinib. Moreover, all five patient respondents cited that they are better able to control their symptoms on larotrectinib than previous forms of therapy. All patient respondents (Thyroid Patient 1, Lung Patient 6 and Salivary Gland Patient 2) reported a significant reduction in side effects compared to previous medications or treatments" (CGR, p. 31)
10	**Clinical Benefit and Patient-Based Values**	**Para 3**	"…the Committee was unable to generalize the overall trial results across all patients with an NTRK gene fusion. In an effort to help facilitate the equitable and timely access to promising treatments for patients while ensuring that treatments considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness and safety, pERC considered potential subgroups of patients with the NTRK gene fusion where a clear unmet need exists despite the associated limitations of the evidence." An unmet need exists among colorectal cancer patients, by way of example, whose 5-year relative survival rate is between 11% and 12%, for Stage IV colon and rectal cancers, respectively. CCC believes that it is unethical to arbitrarily exclude patients based on the frequency of NTRK gene fusions per disease site among those who could otherwise benefit from larotrectinib. This was also evidenced in CCC's feedback in the Clinical Guidance Report (CGR, p. 40).
15	**Adoption feasibility**	**Para 3**	"Due to the high cost of the drug, the considerable uncertainty in the incremental clinical and cost-effectiveness of larotrectinib, pERC concluded that a substantial reduction in

			drug price would be required to improve cost-effectiveness." There is an opportunity for the manufacturer to relieve the cost by participating in a risk sharing agreement, and in order to collect sufficient, robust real-world data through patient support programs and other special access initiatives to provide a full recommendation for reimbursement in additional disease sites. We recommend this as a topic of discussion at deliberations at the Pan-Canadian Pharmacy Alliance.

CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Patient Advocacy Group)

Larotrectinib (Vitrakvi) for NTRK+ solid tumours

Canadian Cancer Survivor Network

October 31, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Larotrectinib
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Canadian Cancer Survivor Network

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Recommendation does not require reconsideration by pERC.	Recommendation should be reconsidered by pERC.

The Canadian Cancer Survivor Network (CCSN) would like to make the following remarks about the pCODR Expert Review Committee (PERC) initial recommendations about Larotrectinib (Vikrakvi).

The Canadian Cancer Survivor Network is disappointed by pERC's recommendation that Larotrectinib only be approved for four very rare cancers. Given that a positive test for TRK fusion cancer is predictive of the success of treatment, CCSN believes that Larotrectinib should have been approved for all eligible patients with TRK fusion cancer.

From pERC's initial recommendation, we understand that "pERC agreed that Larotrectinib aligns with patient values as it improves symptom control, provides better disease control, has a manageable toxicity profile, and provides patients with ease of administration." Given the effectiveness of Larotrectinib in controlling symptoms and its low toxicity, CCSN suggests that all TRK fusion cancers while waiting for trial data to be available in three to four years.

pERC's initial recommendation states that "pERC had considerable concern about the quality of the limited data submitted." CCSN has often suggested that in cases where only limited data can be obtained because the cancers in question are rare or the fact that it is not ethical to conduct randomized clinical trials when a test can identify those who would benefit from the treatment, that enhanced post-marketing surveillance be initiated to facilitate quicker access to treatment.

CCSN strongly recommends that pERC reconsider its recommendation and expand access for adult lung, colorectal, thyroid patients and pediatric patients who have TRK fusion cancers.

PATIENT INTERVIEW

SUMMARY

- Diagnosed with glioblastoma multiform, level 4; given 14.6 months to live
- Started on KETO diet
- Has had chemo and radiation
- Started taking laro in April and have been taking it since (access through SAP)
- At first, liver enzymes went up but adjusted diet, water intake and stayed in ketosis and was able to get them back to normal level
- Is now on liquid laro (approved in Canada)
- Liquid version is much harder on quality of life; has anchored him to his house; capsules were easy to take with him and go; no storage issues; also feels it's better to be able to get three months' supply of capsules (vs one month of liquid)

This patient told us:

"Having laro is critical for me; I don't want to have a moment where I can't get it or take it and we're not fighting the cancer."

"I don't want to see the cancer come back; I want to do everything we can and laro gives us the best shot."

"My quality of life with laro is as easy as taking a vitamin. There was no impact on my life. I was able to go and do things with my kids, stay at a cabin, etc. – that is no longer possible with the liquid."

"I am grateful for laro in any form but from a quality of life perspective, the capsules are 1000% better."

"There's never been a treatment like this before. There's no way I wouldn't recommend access to this drug; other treatments just can't offer the same benefits."

CADTH

pan-Canadian Oncology Drug Review
Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

Larotrectinib (Vitrakvi) for NTRK+ solid tumours

October 31, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Larotrectinib (Vitrakvi). For the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion.
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Patient Group

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1. This evaluation is unfair and inconsistent. The results from the same-pooled data was used to evaluate and deemed acceptable for a positive recommendation for some subgroups but not for the lung cancer subgroup.
2. pERC says it was not satisfied there was a net clinical benefit based on the available evidence. On page 2 of the initial recommendation, pERC gave a positive recommendation to the other sub groups while acknowledging the uncertainty in the evidence. The pooled response rate was 81% and specifically for lung cancer, the rate was 75% (page 16 of the clinician guidance report). STS and pediatric groups who received positive recommendations had ORR's of 88% and 90%, yet lung cancer was not given a positive recommendation. Also the CGP stated these results are generalized applicable to all subtypes. pERC should not apply different standards to evaluate the different subtypes.
3. A lack of unmet need: Treatment with larotrectinib is a need for the lung cancer sub group. This disease comes with a significant disease burden, and the prognostic impact is evident in the patient outcomes following treatment with larotrectinib. The funding request stated that patients eligible for larotrectinib should have no

satisfactory alternative treatments or have progressed following treatment. Patients are typically offered chemotherapy, which is known for its associated toxic effects or immunotherapy, which is known to have reduced efficacy in driver mutation positive cancers.

On page 18, the CGP considered various limitations associated with the available evidence for the use of larotrectinib in patients with NTRK positive solid tumours and agreed that heterogeneity in the patient selection criteria and trial design impacted the interpretability of the pooled analysis. They determined that despite these limitations, the ORR observed with larotrectinib across a wide range of tumours is impressive and consistent, and not previously seen with available therapies. This is particularly meaningful within the population of patients for which there are no effective systemic treatment options, and/or for whom prognosis is poor. Lung cancer remains the most common cancer in Canada, with patients having a high symptom burden and poor prognosis. NTRK fusions are estimated in up to 1% of NSCLC cases and for the subgroup of patients with lung cancer, the response rates observed with larotrectinib (75%) had previously not been seen with other available therapies for NSCLC (chemotherapy 30-40% and immunotherapy 10-45%). This is quite significant and shows the superiority of larotrectinib over other treatment modalities. Patients on this form of treatment have consistently showed improved symptoms, the ability to be independent, functional and physically active. As such, the response rates support the rationale to treat targetable mutations with biomarker based targeted therapy. How equitable is this recommendation if the standards and rationale used to make the decision are unequal. How is this not an unmet need.

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☐ agrees ☐ agrees in part ☒ disagree

The best clinical practice dictates that targetable mutations need to be treated with targeted therapy.

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The typical treatment for NSCLC patient without a targeted mutation is chemotherapy or immunotherapy. Studies have shown that patients who have targeted mutations respond better with targeted therapies than they do with traditional chemotherapy or immunotherapy. That has been shown in randomized studies in EGFR- and ALK-positive lung cancers. Data presented at the just concluded 2019 World Conference on Lung Cancer, also showed that the TRK inhibitor larotrectinib (Vitrakvi) demonstrates significant activity, efficacy and a favorable safety profile.

Taking into account the administration modality and the known toxicities of the current forms of treatment, it is important to provide patients with choices. Not all patients may be able to tolerate the toxic side effects of chemotherapy or immunotherapy may not work in this group of patients. Chemotherapy, for example requires multiple hospital visits for administration as well as treatments for toxicities and delayed effects. Larotrectinib, which is an oral medication, has the potential to save lives, improve survival and provide patients with a better quality of life.

Cost implications: pERC had concerns about the high cost burdens. Negotiations between the PCPA and manufacturers to facilitate a more cost effective option can provide improve adoption feasibility. This can be negotiated along with the implementation NTRK testing in the currently available testing panels. This should not be a barrier to provide patients with larotrectinib. LCC understands these cost concerns, and would encourage the manufacturer and PCPA to negotiate with patients in mind.

LCC asks pERC to reconsider their recommendation for this group of patients as it offers them the chance to live, and live well, and this aligns with patient values. While we approve of the recommendation for the other tumor groups, we believe there is an unmet need for lung cancer patients too.

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Larotrectinib (Vitrakvi) for NTRK+ solid tumours

Neuroblastoma Canada

October 31, 2019

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	larotrectinib
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Patient Group Neuroblastoma Canada

3.1 Comments on the Initial Recommendation

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While we are pleased to see the approval of larotrectinib for four TRK fusions cancer types, we were disappointed that not all TRK fusion cancer indications were approved.

The population of patients with TRK fusion cancers is already small, and have limited treatment options. By restricting access to larotrectinib for only a subset of TRK fusion cancer patients, pERC is establishing a system of inequality and inequity of access to treatment within a unique patient population. By only allowing some patients with TRK fusion cancers to access larotrectinib, pERC has restricted the majority of TRK fusion patients from accessing a treatment which is precision targeted to their cancer type.

TRK fusion cancers are the result of a distinctive biomarker and for the first time, these patients are able to access a treatment which directly targets their cancer's specific mutation. These patients have traditionally experienced surgery, chemotherapy and radiation – all blanket interventions that do not address the unique mutation of TRK fusion cancers. Surgery, chemotherapy and radiation are the slash, poison, and burn of cancer treatments – they are not designed to specifically hone in on the cancer cells and even though they are important, they result in damage to healthy tissue and organs. For children with cancer, these traditional treatments cause a myriad of late-effects as the child ages and enters adulthood. The long-term effects of surgery, chemotherapy and radiation can last an entire lifetime, resulting in daily challenges and impediments, and in too many cases, resulting in life-threatening conditions and early death.

When Colby was diagnosed with thyroid cancer at the age of 12 years old, he was on an elite soccer team – a boy who was always smiling and had mountains of energy. When his cancer came back for a second time a year later, treatment was much harder on him. Surgery and radiation took its toll on his body and his confidence – he quit soccer, stopped socializing with friends, became uninterested in school, gained weight and experienced depression. Colby has had to mature and grow up quickly through his teenage years – much faster than the average boy. Since starting larotrectinib, his tumours have shrunk, he hasn't had many side-effects, and he can live

his life more freely. Colby now has a job, drives his own car, has a strong social circle, and is finding himself again. On larotrectinib, he isn't required to be admitted to the hospital and only goes once a month for his regularly scheduled clinics. For Colby, the recovery from surgery was extremely difficult and when he was undergoing radiation, he couldn't be around his friends. Now, Colby takes larotrectinib in the morning and evening – he is not in-patient, he is not in pain, his tumours are shrinking, and he can be with friends and family. For Colby's parents, the last five years have been tremendously difficult but since their son started larotrectinib, they feel more positive about the future. "It is emotionally draining. You see your child go through so many different challenges and sometimes you can only watch them go down the rabbit hole. You want them to be kids and have that chance at life", Colby's Mom.

As the science shows, larotrectinib does not work in patients who do not have the NTRK gene fusion; however, the level of response for those patients with the NTRK gene fusion is impressive at a 75% overall response rate (ORR), and a 71% ongoing response rate one year later. The side-effects that patients experience on larotrectinib are highly manageable with no patients discontinuing the use of the drug due to adverse events. In addition, responses are seen almost immediately in patients – unlike many traditional treatments that require multiple cycles of therapy before an evaluable response is observed.

The application of larotrectinib is wide, as illustrated by the following comment from Dr. Sébastien Perreault, Pediatric Neurologist at CHU Sainte Justine. "I'm currently following and treating two patients with aggressive glioma cancer currently on larotrectinib. We observed for both patients a complete response after two cycles. They are doing great without significant side effects (only ALT increase for one and none for the other patient). The quality of life is excellent since this is an oral medication and they come only once a month to the hospital".

The Bayer larotrectinib submission heralded a new exemplar of a pharmaceutical company submitting a drug for approval for both adults and children simultaneously. The pediatric indication was not delayed but deemed equally important to be approved at the same time as the adult population, and was not submitted years later or not at all as we see with other drugs. In addition, the submission of larotrectinib was tumour agnostic – it does not focus on only one type of cancer but on a group of cancers with the same mutation. This precision cancer treatment is not narrow in its treatment group but has realized the brilliance of being responsive to multiple cancer types. Larotrectinib is a stellar example of the future of cancer treatment, and hopefully only the start of other cancer agnostic drugs that are to be developed for a wide variety of oncogenic mutations.

The reality is that this is a problem that is big enough that it ***must*** be addressed, but small enough that it ***can*** be addressed. This presents both challenges and opportunities. Since the patient base is small, meaningful advances require innovative approaches. Fortunately, the smaller population size means this is also an ideal area to try to innovative solutions and regulatory approaches.

Bayer has committed to ongoing evidence generation and performance based risk sharing for larotrectinib through follow-on evidence that will be collected in Canada and globally. Patients cannot wait another 3-4 years for data to be collected. Bayer has developed a partnership with the Terry Fox PROFYLE Program – Precision Oncology for Young People. PROFYLE builds on Canada's world-leading expertise in genomics and pediatric oncology through a national precision medicine platform for CAYA cancer patients. The program aims to transform the care of CAYA cancer patients using next-generation molecular sequencing tools and cancer model systems to identify therapeutic targets. Through PROFYLE, oncologists across Canada can enroll young patients (ages 0-29) with relapsed, refractory or very poor prognosis cancers by submitting a tumour sample to profiling centres. PROFYLE democratizes access to genomic sequencing by making sequencing available to young Canadian patients with cancer, regardless of where they live. PROFYLE is composed of a large array of committed scientific and clinical experts from

across Canada that are tackling this challenge using a multi-disciplined and patient-centred approach.

Neuroblastoma Canada encourages CADTH/pERC to reconsider their decision to only approve the use of larotrectinib for a subset of TRK fusion cancers. We recommend that access to larotrectinib be given to all TRK fusion cancers for adult and pediatric patients who are eligible, have locally advanced or metastatic disease, where current therapies are not satisfactory and do not have a known resistance mutation. Larotrectinib is a precedent setting cancer agnostic treatment.

You have the opportunity to change the stories of adults and children with TRK fusion cancers. In our socially responsible and compassionate society there is a place for going the extra mile to support children and their families who are faced with the horrible reality of "incurable". In doing so, we will forward research, advance cures, save lives and change stories.

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