CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Registered Clinician)

Larotrectinib (Vitrakvi) for NTRK+ solid tumours

October 31, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Larotrectinib/NTRK fusion
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Registered Clinician Feedback Cancer Care Ontario

**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

The Breast DAC wishes there were better ways to adjudicate these rare mutational trials which span across cancer sites. There was one only one breast patient on the study (who did not respond based on the waterfall plot – although with such a small sample it is difficult to generalize this). However, the overall results from the trial are very exciting. The DAC understands the pERC recommendation, however, wishes it could develop a more novel real world evidence building platform for these types of medications with potential conditional approval and re-evaluation based on cost effectiveness from a larger data source. As clinicians, the DAC would be interested in accessing the drug if a patient carried the mutation and they had exhausted all other treatment options. However, on a larger scale, the DAC feels there are more important drugs which we would prefer access to help our breast cancer patients.

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.*

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?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would 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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Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, including the provisional algorithm, the criteria for early conversion will be deemed to have not been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

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Name of the Drug and Indication(s):	Larotrectinib/NTRK fusion
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Registered Clinician Feedback Cancer Care Ontario Skin DAC

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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

The CCO Skin DAC agrees with the recommendation, recognizing the limited data supporting the use in melanoma.

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.*

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Larotrectinib (Vitrakvi) for NTRK+ solid tumours

October 31, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and	Larotrectinib for Neurotrophic Tyrosine Receptor Kinase (NTRK) + solid tumours
Eligible Stakeholder Role in Review (Sponsor and/or Organization Providing Feedback	Clinician Medical Oncologist

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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

This feedback is submitted on behalf of Drs. Ron Burkes, Scott Berry, (Ontario), Ralph Wong (Manitoba), Petr Kavan (Quebec), Rachel Goodwin (Ontario), Ravi Ramjeesingh, Jennifer Spratlin (Alberta), Christine Brezden-Mazley (Ontario), Jonathan Loree (BC).

-We agree with initial recommendation of reimbursement of larotrectinib for the treatment of adult and pediatric patients with locally advanced solid tumours that have neurotrophic tyrosine kinase (NTRK) gene fusions.

-However, we STRONGLY DISAGREE with limiting this recommendation to those with salivary gland tumors, adult or pediatric soft tissue sarcomas and pediatric patients with cellular congenital mesoblastic nephroma aor infantile fibrosarcomas. We feel that this distinction made by pERC is arbirtrary and does not reflect the profile of patients treated on trial or the biology of TRK fusion cancers.

- We feel strongly that the recommendation should be tumour-site AGNOSTIC and should be dependent on the presence of the drug target in line with the Health Canada a label. Evidence supports that all TRK fusion cancers have the same oncogenic driver regardless of tissue type and respond to larotrectinib.

-We disagree with the level of uncertainty suggested by pERC regarding the prognostic impact of the NTRK gene fusion and the magnitude of benefit across all tumour types.

-We DO NOT AGREE that funding should be limited to patients in whom the NTRK fusion gene occurs with high frequency. The frequency of NTRK gene fusions is an uncommon event in the more common cancers but this does not suggest that the clinical benefit is any less in these cancer populations.

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

☒ agrees ☐ agrees in part ☐ disagree

Patients should have NTRK gene fusions with metastatic or locally advanced disease where surgical resection is likely to results in severe morbidity and no satisfactory options.

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?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
12	Registered Clinician Input	3	We do not agree that the clinician input suggested that reimbursement be " for patients in whom the NTRK gene fusion occurs with high frequency"

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Larotrectinib (Vitrakvi) for NTRK+ solid tumours

October 31, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Larotrectinib. For the treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring a NTRK gene fusion.
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Clinical Group Lung Cancer Canada

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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

The decision by pERC to recommend access to Larotrectinib for the treatment of NTRK positive disease in four rare cancers is very welcome and represents an important step forward in making precision medicine a reality for more Canadian cancer patients.

Nevertheless, as a lung cancer medical oncologist, I was extremely disappointed to realize that this recommendation does not extend to NTRK positive non-small cell lung cancer cases. On reading the pERC recommendation in full I think there are three assumptions underlying this lack of recommendation that are not well founded.

Unfounded Assumption 1: NTRK positive metastatic NSCLC has a range of therapeutic options including immune therapy.

While great advancement has been made in managing metastatic NSCLC over the last 15 years, this benefit is not universal to NSCLC patients. Although several new agents have been approved and adopted during this period, the benefit is not additive. For example, EGFR positive patients respond well to EGFR TKIs but not to ALK inhibitors. Similarly ALK positive patients respond well to ALK inhibitors but not to EGFR inhibitors. There is no benefit to be obtained in treating either patient group with a small molecular inhibitor of the other class. Once those patients progress through all small molecular inhibitors in that class, their next option is systemic cytotoxic chemotherapy.

The situation is similar for immunotherapy. Despite the adoption of immune checkpoint inhibitors in the setting of metastatic NSCLC, marker positive cancers such as EGFR and ALK positive tumor consistently do poorly when treated with PDL-1 or PD1 inhibition. (This reality was reinforced again at the recent World Lung Cancer conference in Barcelona). The Maziere's study (Ann Oncol 2019; 1321-28) illustrated that all lung cancer with driver mutation had poor response and PFS on immunotherapy regardless of PDL-1 expression. Gatalacia (Modern Pathology 2019;32:147-53) reported NTRK fusion positive cancers harbor only this molecular abnormality and can therefore not be treated with other targeted agents. In this analysis, only 20% or so had meaningful PDL-1 expression and their Tumour Mutation Burden was low. These are all predictors for poor benefit to immunetherapy. All indications are that NTRK positive tumours are very likely to behave like EGFR and ALK positive cases, responding well to the appropriate NTRK inhibitor (such as larotrectinib) but not to immunotherapy.

In summary. This means that without Larotrectinib availability, options for NTRK positive NSCLC patients are sparse and essentially unchanged in almost 2 decades.

Unfounded Assumption 2: NTRK positive metastatic NSCLC is not an unmet need. Metastatic NSCLC is currently incurable and in the absence of a prolonged immunotherapy-induced disease control, is associated with a life expectancy of 12 -14 months. NTRK positive cases do not have other precision oncology therapies and are unlikely to benefit from immunotherapy. Clearly, these features seem to fulfill the definition of an "unmet clinical need". A lack of data to define the specific clinical course of NTRK positive cases does not change that reality.

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

☐ agrees ☐ agrees in part ☒ disagree

Unfounded Assumption 3: the pharmaco economic impact of identifying NTRK positive tumours is prohibitive.

The frequency of the NTRK gene fusion in a given histology does not affect the clinical efficacy of larotrectinib. While the incidence of NTRK positive cases influences the cost of screening and identifying NTRK positive patients, the efficacy of Larotrectinib in that setting remains the same. As such, I do not believe that the somewhat inflated costs of NTRK screening used for these calculations should influence a decision that should be based on clinical benefit.

Even if it is insisted that the NTRK testing costs must be included in the equation, four important factors need to be incorporated into the calculations:

(a) the cost of NGS testing is decreeing and continues to do so as the throughput of samples being tested increases. In the near term, it is very likely that NTRK testing can be carried out for $500 per sample rather than $3000 per sample.

(b) NGS panel based testing is likely to become an expected standard of care in an increasing number of centers across Canada over the next 24 months. As the number of genes that need to be tested for increases and the range of histologies in which mutation testing becomes relevant grows, it will become more economical to do a single panel-based test where a range of mutations are tested for in parallel rather than sequentially

as is currently the case. At that point, NTRK positive cases will become routinely identifiable across the country.

(c) Many patients will insist on having their tumor samples profiled by Foundation One or Guardant Health at no cost at the health care system.

(d) Our own cost analysis (University of Calgary POET program) for NTRK screening for Alberta for all cases of metastatic NSCLC in the 1st line setting would total $750,000 per year using a process that incorporates an IHC based screening step. If reserved for 2nd line testing only and a 40% attrition rate for 1st to 2nd line treatment is assumed, the cost falls to less than $300,000 per year. This is profoundly less than the $80M per year calculated in the economic analysis and very much in line with the $285,000 per year recommendation for larotrectinib in the 2nd line setting.

Finally, it seems to me that a slight inconsistency in this recommendation calls into question the ethics of recommending access to Larotrectinib for NTRK positivity at high prevalence in some rare histologies and not for NTRK positivity at a low prevalence in common histologies.

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?

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Name of the Drug and Indication(s):	Larotrectinib
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Clinical Organization Pediatric Oncology Group of Ontario

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

☐ agrees ☒ agrees in part ☐ disagree

While we agree with the funded recommendations for pediatric patients, we do not feel this list is complete.

We believe that based on the data and the large number of different histology tumor types that harbor trk fusions a histology agnostic approach has the most support /evidence.

Specifically, in the case of pediatrics two important diagnoses have been excluded in the current approval. These are Radioiodine (RAI) resistant papillary thyroid cancer (trk fusion positive) and CNS tumors with trk fusion. These are two diagnoses in which there are not sufficient alternative therapies. For RAI resist-PTC there are no other options that have shown significant response however, the responses reported with larotrectinib in the trk fusion positive subset were significant, including patients with metastatic disease. Similarly for CNS trk positive tumors , which are often identified in younger patients including toddlers and infants, the current treatments of radiation and chemotherapy are often ineffective and long term side effects (esp for less than 3 yrs of age) are often devastating. This group has and will benefit from larotrectinib similar to the pediatric patients with other trk + tumors.

While these are small patient and rare populations, they have no other satisfactory treatment options and their rarity suggests definitive clinical trials are unlikely to be realized.

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

☐ agrees ☐ agrees in part ☐ disagree

N/A

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?

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1 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC), including the provisional algorithm. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, pERC makes an Initial Recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation. It should be noted that the Initial Recommendation, including the provisional algorithm may or may not change following a review of the feedback from stakeholders.

pERC welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The Stakeholder Feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the Initial Recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part or disagrees with the Initial Recommendation, and to provide a rational for their response.

   Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder can still support the recommendation proceeding to a Final Recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a Final Recommendation ("early conversion")?**

   An efficient review process is one of pCODR's key guiding principles. If all eligible stakeholders support the Initial Recommendation proceeding to a Final Recommendation and that the criteria for early conversion as set out in the *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website two (2) Business Days after the end of the feedback deadline date. This is called an "early conversion" of an Initial Recommendation to a Final Recommendation.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), including the provisional algorithm as part of the feasibility of adoption into the health system, the criteria for early conversion will be deemed to have **not** been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. If the substantive comments relate specifically to the provisional algorithm, it will be shared with PAG for a reconsideration. Please note that if any one of the eligible stakeholders does not support the Initial Recommendation proceeding to a Final pERC Recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the Initial Recommendation. Please also note that substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the Initial Recommendation. If the feedback can be addressed editorially this will done by the CADTH staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting. Similarly if the feedback relates specifically to the provisional algorithm and can be addressed editorially, CADTH staff will consult with the PAG chair and PAG members.

The Final pERC Recommendation will be made available to the participating federal, provincial and territorial ministries of health and provincial cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

2 Instructions for Providing Feedback

a) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:
   - The Sponsor making the pCODR Submission, or the Manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - The Provincial Advisory Group (PAG)

b) The following stakeholders are eligible to submit Feedback on the provisional algorithm:
   - The Sponsor making the pCODR Submission, or the Manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - The Board of Directors of the Canadian Provincial Cancer Agencies

c) Feedback or comments must be based on the evidence that was considered by pERC in making the Initial Recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

d) The template for providing *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

e) At this time, the template must be completed in English. The Stakeholder should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply.

f) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½" by 11" paper. If comments submitted exceed three pages, only the first three pages of feedback will be provided to the pERC for their consideration.

g) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the

recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the Initial Recommendation, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.

h) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR program.

i) The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.

j) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca

Note: CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.