CADTH

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

Larotrectinib (Vitrakvi) for NTRK+ solid tumours

October 31, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): *VITRAKVI® (Larotrectinib) for TRK fusion cancer*
Eligible Stakeholder Role in Review *Submitter*

Organization Providing Feedback *Bayer Inc.*

3.1 Comments on the Initial Recommendation

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

☒ Disagree

While Bayer acknowledges that pERC made a positive recommendation in four very rare tumour types, Bayer respectfully disagrees with not extending access to all eligible patients with TRK fusion cancer. This limited recommendation causes inequity for TRK fusion cancer patients and significant ethical concerns. Bayer requests that pERC considers the following:
1) Patient Based-Values: pERC acknowledged that larotrectinib aligned with patient values, but these values came from interviews with multiple larotrectinib patients representing tumours outside of the four recommended tumour types. Bayer requests that the final recommendation: i) ensures equity of access that reflects a TRK fusion cancer patient's equity of merit based on high unmet need, lack of satisfactory treatment alternatives, and poor prognosis; ii) represents the entirety of the values expressed by the patient groups' input. Otherwise, implicated stakeholders are left without adequate justification for the differential approach to the various tumours.

2) Clinical Benefit: *NTRK* gene fusion frequency is an inappropriate criterion for selecting and excluding tumours. Moreover, the stated criteria (*NTRK* frequency and prognostic implications, and the merit criteria listed above), along with an unstated expectation of efficacy by tumour type, were inconsistently applied in order to select tumours. Examples such as RAI-R thyroid, GIST, and treatment-resistant NSCLC should have met pERC's stated criteria. In contrast, the CGP "believed there is an unmet need for better therapies in adult and pediatric patients with NTRK-gene fusion advanced solid cancers that either have no satisfactory alternative therapies or have exhausted currently available standard therapies."[1] The CGP recommended that "**careful consideration be given to reimbursement criteria so that patients who could potentially benefit from larotrectinib are not excluded.**"[2] In granting an unprecedented tumour-agnostic NOC/c for *all* eligible TRK fusion cancer patients, Health Canada fulfilled its stated objective to provide earlier access to *promising* new drugs for patients suffering from serious, life-threatening or severely debilitating diseases or conditions for which no drug is presently marketed.

3) Economic Evaluation: The CGR/EGR overestimated *NTRK* gene fusion testing volumes when compared to those developed by the national CANTRK working group of Canadian oncologists and pathologists. NSCLC and CRC were overestimated by **3-4 times**. The CGR/EGR did not consider IHC screening to manage costs, and inappropriately allocated the full cost of NGS to larotrectinib, even though an NGS panel would interrogate for multiple targets, replace other tests, and ultimately provide value if any actionable oncogenic target were identified.

4) Adoption Feasibility: Real-world evidence development and performance-based risk-sharing are fair and viable alternatives to waiting 3-4 years for final trial data to resubmit. It would avoid the inequity caused by the exclusion of the majority of patients in the initial recommendation.

Through Bayer's patient support program, response to treatment can be ascertained and monitored at an ***individual*** patient level, such that only those patients that respond are reimbursed. The median time to response is only 1.8 months, allowing for quick confirmation and certainty of

benefit. Through Canadian real-world evidence initiatives articulated in Bayer's submission (PROFYLE and the ON-TRK non-interventional study), equitable access is possible while generating confirmatory TRK fusion cancer evidence. However, this initial recommendation makes the generation of such evidence infeasible due to low patient volumes (<10 eligible patients/year).

Bayer is concerned with the consequences for Canadian TRK fusion cancer patients. Examples which align to the pERC criteria of unmet need, few alternatives, and poor prognosis, but would be ineligible based on this recommendation are:

- Nine year-old Ashton Leeds[3,4], an Albertan with stage 4, RAI-refractory thyroid TRK fusion cancer, who upon entering the SCOUT trial had poor prognosis and high unmet need. He responded well to larotrectinib and continues to do well.
- Three (out of five) *NTRK* gene fusion patients with NSCLC, mesothelioma, and primary CNS tumours have accessed larotrectinib through Health Canada's Special Access Program (SAP). By definition, the SAP is for patients with poor prognosis and no treatment options.

These patients have equal merit to those eligible under the initial pERC recommendation.

Bayer requests that pERC expand larotrectinib access to all eligible patients that have a solid tumour with a confirmed NTRK gene fusion without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, have no satisfactory treatment options, and have demonstrated a response to treatment. In particular, Bayer urges pERC to consider access for thyroid, lung, colorectal, GIST and CNS cancer patients of all ages who meet these criteria. In doing so, pERC would provide more equitable access to larotrectinib for all eligible patients harbouring an *NTRK* gene fusion at the point of equal merit.

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?

P #	Section Title	Para, Line #	Comments and Suggested Changes to Improve Clarity
4	Summary of pERC…	3, 5	pERC noted that patients could be replaced in the NAVIGATE trial… pERC expressed concern that this may have introduced bias...

Bayer confirms that no patient was replaced in NAVIGATE, 14001 or SCOUT and hence no bias was created. Specifically for NAVIGATE, since version 7 of the trial protocol (24 JUL 2017), no patient could be replaced. Reviewers did not raise this concern for clarification prior to pERC deliberation.

3.2 Comments Related to Eligible Stakeholder Provided Information

☒ Do not support conversion to Final Recommendation.
Recommendation should be reconsidered by pERC.

P #	Section Title	Para, Line #	Comments related to Stakeholder Information
4 10	Summary of pERC…	3, 11, 2, 5	pERC was unable to generalize the overall trial results across all tumour types…all patients with an *NTRK* gene fusion.

-A basket trial design does not support assessment by individual tumor type. The CGP recognized this, stating: "given the rarity of *NTRK* fusions…a basket trial, single-arm design is justifiable"[5] and, "from a histology-agnostic, biomarker-driven perspective, larotrectinib offers a clinical benefit."[6]
-*NTRK* fusion proteins are oncogenic drivers across tumour types as they have transformational activity, including tumorigenic capacity.[7-13] The Sorensen laboratory in British Columbia and others have shown that the expression of *ETV6-NTRK3* in human cell (i.e. fibroblast, kidney, and breast) and animal models is by itself tumorigenic.[7-13] Expression of *ETV6-NTRK3* in normal human (breast) epithelial cells makes them tumorigenic.[14] Collectively, this confirms that *NTRK* fusion proteins are oncogenic drivers responsible for both the initiation and maintenance of cancer.[7-13]

2	Initial Recommendation	2, 2	pERC…was not satisfied that there is a net clinical benefit…there was considerable uncertainty regarding the prognostic impact of the *NTRK* gene fusion and the magnitude of clinical benefit across all tumour types

-Tumour staging and failure of prior line(s) of therapy are sufficient prognostic factors to qualify poor prognosis and high unmet need, even in the absence of *NTRK* natural history data. Larotrectinib demonstrated benefit across tumours types. Examples from the submitted ESMO 2018, n=122 data set (larotrectinib ORR, 95% CI, sample size):
Advanced RAI-R thyroid: mean life expectancy: 3-5 years[15]; ORR:81% (54%, 96%, n=16)[16]
GIST: 5-year survival rates for GIST with distant metastases: 52%[17]; ORR:100% (48%, 100%, n=5)[16]
NSCLC: 40% diagnosed at stage IV, 5-year survival rate: <10%[18]; ORR:71% (29%, 96%, n=7)[16]
CRC: 5-year relative survival: 11% for stage IV colon cancer[18]; ORR: 50% (12%, 88%, n=6)[16]
Primary CNS: For all ages, 5-year survival rate: <25%[19]; ORR: 36% (13%,65%), with 14% CR (n=14)[16]
-pERC acknowledged the "large and impressive"[20] ORR across a wide variety of tumour types and the 28.3-month ongoing PFS (median follow-up of 19.6 months). Bayer provided context by evaluating the progression-free survival ratio (PFSr), a direct intra-patient evaluation of treatment benefit. A PFS2/PFS1 ratio >1.3 reflects clinically-meaningful treatment benefit.[21] While PFS is ongoing for many larotrectinib patients, **65%** of patients had attained a PFSr≥1.3 in the ePAS (n=73) dataset. This PFSr comparison helps address pERC's concerns of heterogeneity of tumour type.

2 4	Summary of pERC…	1, 13 3, 18	pERC agreed that larotrectinib aligns with patient values; … tumours that harbour a high frequency of the NTRK gene fusion…who may have more certainty of clinical benefit…

-Frequency of *NTRK* gene fusion in a given tumour type has no bearing on the efficacy of larotrectinib and should not be used as a selection criterion. Denying an *NTRK* positive patient access to a targeted treatment because the fusion is infrequent in patients who share the same tumour histology is not equitable. Moreover, application of this criterion was inconsistent: pERC recommended coverage for adult STS, where *NTRK* frequency is only 0.5-2.0%, but not for thyroid with a higher frequency of 1.5%-12%. The thyroid subgroup had high ORRs (see above) and the same sample size as IFS (n=16), and similar to salivary (n=18). NSCLC has *NTRK* frequency similar to STS, high ORR results (see above), and larger sample size than CMN (NSCLC, n=7; CMN, n=1).

6	Summary of pERC…	1, 1	pERC considered the feasibility of implementing…and discussed… NTRK gene fusion could result in a potentially large budget impact.

-Bayer's submitted diagnostic algorithms and testing volume estimates developed by the CANTRK group contrast with the CGR/EGR overestimates. They documented judicious *NTRK* testing, incorporating it into existing testing algorithms, in later stages or after failure of standard therapies, or after exclusion of other more common genomic aberrations. For example:
-In NSCLC, the CANTRK estimates **~5,000** patients eligible for *NTRK* testing (based on ~7,000 stage 3/4 patients who see a medical oncologist with ~80% having non-squamous or poorly differentiated adeno-squamous histology). This is significantly less than 18,966 estimated in the CGR/EGR.
-In CRC, of the 26,800 incident patients, CANTRK recommended stage 4 patients only be screened using IHC (followed by NGS), representing 20% or **~5,300** patients vs. 12,900 as per the CGR/EGR.
-Bayer is also supporting the CANTRK Ring Study to establish high quality testing among 17 Canadian pathology and molecular diagnostic laboratories in their pan-TRK IHC screening assay and NGS-based technologies to detect *NTRK* gene fusions in clinical testing.

3	Next Steps	1, 6	…to manage both the patient population and the budget impact of a reimbursement recommendation for larotrectinib.

-Bayer notes the US uptake of larotrectinib since launch is in-line with what was submitted in the Canadian BIA. In contrast, the EGR estimated up to ~1,130 patients/year for Canada. Translating this EGR estimate to the US, which has a more advanced testing infrastructure, would exceed the total US epidemiological estimates for TRK fusion cancer patients (~2500-3000).
- On Sept 16th, 2019, Bayer launched FastTRK, a complimentary *NTRK* gene fusion testing program. Currently, Bayer has partnered with LifeLabs and the Kingston Health Sciences Centre to provide *NTRK* gene fusion testing services for Canadians until at least the end of 2021.

Works Cited

1. pan-Canadian Oncology Drug Review. August 29, 2019. Initial Clinical Guidance Report. Larotrectinib (Vitrakvi) for Neurotrophic Tyrosine Receptor Kinase (NTRK) Positive Solid Tumours. page 15, paragraph 6, line 1.
2. pan-Canadian Oncology Drug Review. August 29, 2019. Initial Clinical Guidance Report. Larotrectinib (Vitrakvi) for Neurotrophic Tyrosine Receptor Kinase (NTRK) Positive Solid Tumours. page.20, paragraph 2, line 4.
3. Ward RCN. Alberta boy with thyroid cancer runs, plays after taking U.S.-approved drug. Posted: Dec 05, 2018. Last Updated: December 6, 2018.
4. Kurs L. Matched to the Perfect Target, Drug Dramatically Shrinks Tumors in All Ages, Multiple Cancers. *Seattle Children's Hospital Website*. February 21, 2018.
5. pan-Canadian Oncology Drug Review. August 29, 2019. Initial Clinical Guidance Report. Larotrectinib (Vitrakvi) for Neurotrophic Tyrosine Receptor Kinase (NTRK) Positive Solid Tumours. page 15, paragraph 7, line 4.
6. pan-Canadian Oncology Drug Review. August 29, 2019. Initial Clinical Guidance Report. Larotrectinib (Vitrakvi) for Neurotrophic Tyrosine Receptor Kinase (NTRK) Positive Solid Tumours. page 18, paragraph 6, line 1.
7. Cetinbas N, Huang-Hobbs H, Tognon C, et al. Mutation of the salt bridge-forming residues in the ETV6-SAM domain interface blocks ETV6-NTRK3-induced cellular transformation. *The Journal of biological chemistry*. Sep 27 2013;288(39):27940-27950.
8. Park J, Kim J, Park B, et al. Novel identification of STAT1 as a crucial mediator of ETV6-NTRK3-induced tumorigenesis. *Oncogene*. Apr 2018;37(17):2270-2284.
9. Tognon C, Garnett M, Kenward E, Kay R, Morrison K, Sorensen PH. The chimeric protein tyrosine kinase ETV6-NTRK3 requires both Ras-Erk1/2 and PI3-kinase-Akt signaling for fibroblast transformation. *Cancer research*. Dec 15 2001;61(24):8909-8916.
10. Tognon C, Knezevich SR, Huntsman D, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. *Cancer cell*. Nov 2002;2(5):367-376.
11. Tognon CE, Rafn B, Cetinbas NM, et al. Insulin-like growth factor 1 receptor stabilizes the ETV6-NTRK3 chimeric oncoprotein by blocking its KPC1/Rnf123-mediated proteasomal degradation. *The Journal of biological chemistry*. Aug 10 2018;293(32):12502-12515.
12. Tognon CE, Somasiri AM, Evdokimova VE, et al. ETV6-NTRK3-mediated breast epithelial cell transformation is blocked by targeting the IGF1R signaling pathway. *Cancer research*. Feb 1 2011;71(3):1060-1070.
13. Wai DH, Knezevich SR, Lucas T, Jansen B, Kay RJ, Sorensen PH. The ETV6-NTRK3 gene fusion encodes a chimeric protein tyrosine kinase that transforms NIH3T3 cells. *Oncogene*. Feb 17 2000;19(7):906-915.
14. Unpublished, personal communication with Dr. Sorensen and Dr. Eaves. 2018-2019.
15. Durante C, Haddy N, Baudin E, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. *The Journal of clinical endocrinology and metabolism*. Aug 2006;91(8):2892-2899.
16. Bayer Inc. 2019. Larotrectinib pCODR submission.
17. American Cancer Society. Survival Rates for Gastrointestinal Stromal Tumors. https://www.cancer.org/cancer/gastrointestinal-stromal-tumor/detection-diagnosis-staging/survival-rates.html. Accessed on September 12, 2019.
18. Canadian Cancer Statistics. A 2018 special report on cancer incidence by stage.
19. Mao Y, Robson D, Semenciw RM, Morrison HI, Wigle DT. Long-term survival rates among patients with cancer in Saskatchewan, 1967-1986. *Canadian journal of public health = Revue canadienne de sante publique*. Nov-Dec 1991;82(6):413-420.
20. pan-Canadian Oncology Drug Review Expert Review Committee (pERC). August 29, 2019. Initial Recommendation. Larotrectinib (Vitrakvi) for Neurotrophic Tyrosine Receptor Kinase (NTRK) Positive Solid Tumours. page 4, paragraph 2, line 6.

21. Von Hoff DD. There are no bad anticancer agents, only bad clinical trial designs--twenty-first Richard and Hinda Rosenthal Foundation Award Lecture. *Clinical cancer research : an official journal of the American Association for Cancer Research*. May 1998;4(5):1079-1086.