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pan-Canadian Oncology Drug Review
Initial Economic Guidance Report

Larotrectinib (Vitrakvi) for Neurotrophic Tyrosine Receptor Kinase (NTRK) Positive Solid Tumours

August 29, 2019

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This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.
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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis (seven separate models: one 'pooled' analysis, 6 tumor-specific analyses) submitted to pCODR by Bayer Inc. compared larotrectinib to current standard of care (varying according to tumor type) for adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion (summarized in Table 1). This is consistent with the submitter's funding request.

Table 1. Submitted Economic Model

Reimbursement Request/Patient Population Modeled	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. The patient population modeled matches the reimbursement request
Type of Analysis	*Cost-utility analysis (CUA) and cost-effectiveness analysis (CEA)*
Type of Model	*Partitioned-survival*
Comparator	*7 separate analyses included in the base case:* *1 'pooled' analysis comparing to Best Supportive Care (BSC) for each of the 14 tumor types included in the integrated analysis from three clinical trials informing the efficacy and safety outcomes* *6 tumor-specific analysis:* • *colorectal cancer (CRC - comparators: trifluridine plus tipiracil; BSC);* • *Non-Small Cell Lung Cancer (NSCLC - comparators: pembrolizumab plus platinum; nivolumab; BSC);* • *melanoma (comparator: BSC);* • *thyroid cancer (comparators: lenvatinib; BSC);* • *adult Soft Tissue Sarcoma (STS - comparator: BSC);* • *Pediatric STS (comparator: BSC).*
Year of costs	*2018*
Time Horizon	*5 years*
Perspective	*Canadian publicly-funded health system*
Cost of larotrectinib	Larotrectinib costs $5,988.89 per bottle for a bottle of 56 capsules (25 mg strength); $17,966.67 for a bottle of 56 capsules (100mg strength);; and $8,555.56 per 100 mL oral solution (20 mg/mL). In adults and at the recommended dose of 100mg twice per day, larotrectinib costs: • $641.67 with the 100 mg capsule (2 x 100mg capsule) or $855.56 with the 25 mg capsule (8 x 25mg 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: • maximum of $855.56 per day. Per 28-day course: 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.

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Cost of standard of care per tumor type ** Price Source: pCODR reviews (as cited by the submitter)*	Per 28-day course 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-sunitib): $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 (capeticabine-epirubicin-doxorubicin-fulvestrant): $1,589 Appendix: • BSC (capecitabine-5-fluorouracil-irinotecan-raltritrexed-oxaliplatin-leucovorin-folinic acid): $3,225 Pancreatic: • BSC (5-fluorouracil-gemcitabine): $181
Model Structure	The partitioned-survival model comprised 3 health states: pre-progression, post-progression, and death. The cycle length was 28 days. The proportion of patients in each health state at any timepoint was informed by the survival curve analysis. Survival benefit beyond observed values was extrapolated through parametric curve fitting. Costs, life-years and QALYs were estimated from probabilistic analysis.
Key Data Sources	Larotrectinib efficacy and safety evidence came from an integrated analysis of 3 studies (LOXO-TRK-14001, LOXO-TRK-15002 or NAVIGATE, LOXO-TRK-15003 or SCOUT) in a total of 73 adult and pediatric patients. The efficacy and safety for the comparators came from representative studies selected by the manufacturer to characterize the range of potential outcomes associated with the comparators. No formal quantitative indirect treatment comparison was performed.

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1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparisons presented are appropriate. Relevant issues identified included:

- From a histology-agnostic, biomarker-driven perspective, larotrectinib offers the potential for clinical benefit in good performance status adult and pediatric patients with advanced solid tumours that harbour an NTRK-gene fusion.
- There is likely more certainty of benefit among populations for whom the burden of illness and/or need for effective therapeutic agents is high.
    - Among pediatric patients with NTRK+ advanced solid cancers and adult patients with NTRK+ advanced solid cancers who have an unfavourable prognosis and limited therapy options, the CGP concluded that there is a net clinical benefit
    - Among adult patients with an NTRK+ advanced solid cancers who have relatively better prognosis and/or better alternative systemic therapy options, the CGP concluded that there may be a net clinical benefit as they were unable to determine the magnitude of clinical benefit attributable to larotrectinib given the availability of alternative treatment options for whom comparative evidence was unavailable.
- The CGP considered various limitations associated with the available evidence for the use of larotrectinib. Despite these limitations, the CGP agree that the ORR observed with larotrectinib across a wide range of tumours is impressive and consistent, and not previously seen with available therapies.
- Although some variation was observed in response rates within the subgroup analysis by tumour type, the panel agreed that the overall pooled analysis results are generalizable to all patients with advanced solid cancers harbouring an NTRK fusion.
- The CGP acknowledged that the pooled KM curves for PFS and OS are methodologically difficult to interpret. In addition, the CGP acknowledged that ORR is not a validated surrogate for PFS and OS. However, the CGP agreed that meaningful and durable response rates are likely to translate into PFS benefit and in patients with limited post-progression options, further likely to translate to OS benefit.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered the potential for significant improvement beyond current standard options, the route of administration and the lack of chemotherapy related toxicity as important benefits of larotrectinib which could be attractive for patients with co-morbidities where cytotoxic chemotherapy is contraindicated. However, registered clinicians noted the paucity of evidence as a barrier to displacement of more established therapies. All clinicians agreed that patients eligible for larotrectinib would need to present with solid tumours harbouring the NTRK gene fusion. There was no consensus on the timing of testing nor the sequencing of larotrectinib compared to currently available agents. The model considered these factors by including overall survival, progression-free survival, adverse events, the oral route of administration and, quality-of-life. For most cancer types, larotrectinib is compared to BSC, consistent with a last resort option. The model also incorporated various technologies for testing including next-generation sequencing (NGS), DNA and/or RNA sequencing, fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), and reverse transcription polymerase chain reaction (RT-PCR).

Summary of patient input relevant to the economic analysis
Patient input was obtained from 12 patients experienced with larotrectinib and two caregivers via an online survey or telephone interview. All patient respondents were NTRK+, had received previous therapies and had varying symptoms affecting their daily life. Patients hope for

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improved outcomes on symptoms, pain, mobility, ease of breath, survival, and quality-of-life with a targeted therapy such as larotrectinib. Ease of administration (oral formulation) in the comfort of their home is appreciated. Adverse events were considered relatively minor and tolerable. According to the patient respondents, larotrectinib has delivered a meaningful response in their cancer while maintaining a high level of quality-of-life. The model has captured patients' values through the inclusion of overall survival and progression-free survival, important outcomes for patients. The model also included oral administration, adverse events, and quality-adjusted life-years.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for larotrectinib which are relevant to the economic analysis: place in therapy for larotrectinib, additional health care resources that may be required to monitor or treat toxicities, number of patients requiring NTRK gene fusion testing, and access to NTRK gene fusion testing. Furthermore, PAG recognized that there is no single standard of care for the targeted population and that treatment is currently dependent on the specific type of solid tumor. For patients who have progressed on all available treatment options, BSC would be the only option left. The model addresses larotrectinib place in therapy by considering its use as a last resort option for most tumour types (i.e., comparing to BSC), except for NSCLC, CRC and thyroid cancer where some of the comparators are more compatible with an earlier stage of treatment in patients with advanced disease. Adverse event costs are included in the economic model. The frequency of NTRK fusion is uncertain. The necessity of NTRK gene fusion testing is included in the model. However, the impact of access to testing cannot be included in a cost-effectiveness analysis or budget impact analysis.

1.3 Submitted and EGP Reanalysis Estimates

In the manufacturer's base case (versus BSC; 5-year horizon), the incremental costs varied from $124,182 in CRC to $737,719 in pediatric STS. Incremental life-years varied from 0.604 life-year gained in melanoma to 1.36 in NSCLC while the QALY gain varied from 0.425 QALY in melanoma to 0.986 QALY in adult STS. Consequently, the ICUR varied from $261,580 per QALY for CRC to $1,125,918 per QALY for pediatric STS. The major driver of costs for all tumor types was treatment and diagnostic costs and the major driver of benefit was the QALY gain in the pre-progression phase. Analyses against other comparators in NSCLC, CRC and thyroid gave similar results. A summary of manufacturer's and EGP results is presented in

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Table *2*.

The manufacturer's report indicated that the results were sensitive to the time horizon and the inclusion or exclusion of diagnostic costs. All other scenario analyzed (e.g., inclusion of indirect costs, variation of adverse event costs, using the 'pooled' survival curves in the tumour-specific analyses, etc.) had a much smaller impact on the ICUR.

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Table 2. Submitted and EGP estimates for health economic outcomes

Estimates (range/point)	Submitted	EGP Reanalysis (without testing)	EGP Reanalysis (NGS screening and high NTRK frequency)	EGP Reanalysis (NGS screening and low NTRK frequency)
'Pooled analysis'*				
ΔE (LY)	1.222			
Progression-free	1.276		---	
Post-progression	-0.053		---	
ΔE (QALY)	0.833			
Progression-free	0.866		---	
Post-progression	-0.032		---	
ΔC ($)	$415,167			
ICER estimate ($/QALY)	$499,577		---	
CRC: larotrectinib versus trifluridine plus tipiracil				
ΔE (LY)	0.522		0.53	
Progression-free	0.230		0.18	
Post-progression	0.293		0.35	
ΔE (QALY)	0.405		0.40	
Progression-free	0.223		0.19	
Post-progression	0.182		0.22	
ΔC ($)	$141,403	$85,725	$123,214	$460,714
ICER estimate ($/QALY)	$347,865	$214,079	$310,000	$1,156,944
CRC: larotrectinib versus BSC				
ΔE (LY)	0.674		0.65	
Progression-free	0.333		0.31	
Post-progression	0.342		0.34	
ΔE (QALY)	0.474		0.45	
Progression-free	0.261		0.24	
Post-progression	0.213		0.21	
ΔC ($)	$124,182	$77,359	$114,840	$452,340
ICER estimate ($/QALY)	$261,580	$169,381	$256,000	$1,010,149
NSCLC: larotrectinib versus pembrolizumab plus platinum				
ΔE (LY)	0.719		0.50	
Progression-free	0.792		0.64	
Post-progression	-0.073		-0.14	
ΔE (QALY)	0.512		0.38	
Progression-free	0.549		0.45	
Post-progression	-0.038		-0.07	
ΔC ($)	$89,241	$20,609	$58,121	$395,621
ICER estimate ($/QALY)	$174,310	$70,619	$165,771	$983,130
NSCLC: larotrectinib versus nivolumab				
ΔE (LY)	1.215		1.02	
Progression-free	1.231		1.07	
Post-progression	-0.015		-0.05	
ΔE (QALY)	0.780		0.66	
Progression-free	0.792		0.69	
Post-progression	-0.012		-0.03	
ΔC ($)	$306,819	$241,169	$278,677	$616,177
ICER estimate ($/QALY)	$393,467	$368,371	$424,569	$920,177

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Estimates (range/point)	Submitted	EGP Reanalysis (without testing)	EGP Reanalysis (NGS screening and high NTRK frequency)	EGP Reanalysis (NGS screening and low NTRK frequency)
NSCLC: larotrectinib versus BSC				
ΔE (LY)	1.36	1.22		
Progression-free	1.051	0.92		
Post-progression	0.31	0.30		
ΔE (QALY)	0.83	0.74		
Progression-free	0.689	0.60		
Post-progression	0.142	0.14		
ΔC ($)	$363,554	$304,447	$341,943	$679,443
ICER estimate ($/QALY)	$437,848	$416,294	$466,665	$918,383
Melanoma: larotrectinib versus BSC				
ΔE (LY)	0.605	0.44		
Progression-free	0.581	0.68		
Post-progression	0.024	-0.25		
ΔE (QALY)	0.426	0.32		
Progression-free	0.415	0.49		
Post-progression	0.015	-0.17		
ΔC ($)	$175,988	$190,509	$228,031	$565,531
ICER estimate ($/QALY)	$413,987	$597,750	$716,851	$1,796,431
Thyroid: larotrectinib versus lenvatinib				
ΔE (LY)	0.956	0.92		
Progression-free	0.844	0.71		
Post-progression	0.011	0.21		
ΔE (QALY)	0.777	0.70		
Progression-free	0.721	0.61		
Post-progression	0.056	0.09		
ΔC ($)	$402,594	$345,592	$353,103	$378,212
ICER estimate ($/QALY)	$518,193	$505,913	$519,865	$555,857
Thyroid: larotrectinib versus BSC				
ΔE (LY)	0.791	0.63		
Progression-free	1.28	1.15		
Post-progression	-0.489	-0.52		
ΔE (QALY)	0.827	0.70		
Progression-free	1.068	0.96		
Post-progression	-0.241	-0.27		
ΔC ($)	$438,398	$406,083	$413,582	$538,691
ICER estimate ($/QALY)	$529,936	$541,087	$551,949	$586,167
Adult STS: larotrectinib versus BSC				
ΔE (LY)	0.976	0.89		
Progression-free	1.077	1.04		
Post-progression	-0.102	-0.16		
ΔE (QALY)	0.986	0.95		
Progression-free	1.012	0.99		
Post-progression	-0.026	-0.04		
ΔC ($)	$401,714	$398,988	$436,496	$548,996
ICER estimate ($/QALY)	$407,242	$421,888	$461,363	$580,830
Pediatric STS (> 2 years of age): larotrectinib (full dose) versus BSC				
ΔE (LY)	1.085	1.54		

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Estimates (range/point)	Submitted	EGP Reanalysis (without testing)	EGP Reanalysis (NGS screening and high NTRK frequency)	EGP Reanalysis (NGS screening and low NTRK frequency)
Progression-free	1.001	1.39		
Post-progression	0.084	0.15		
ΔE (QALY)	0.655	0.91		
Progression-free	0.622	0.86		
Post-progression	0.033	0.05		
ΔC ($)	$737,719	$1,220,570	$1,258,050	$1,370,550
ICER estimate ($/QALY)	$1,125,918	$1,295,244	$1,341,143	$1,470,870
Pediatric STS (≤ 2 years of age): larotrectinib (half dose) versus BSC				
ΔE (LY)	---	1.54		
Progression-free		1.39		
Post-progression		0.15		
ΔE (QALY)	---	0.91		
Progression-free		0.86		
Post-progression		0.05		
ΔC ($)	---	$731,685	$732,386	$732,469
ICER estimate ($/QALY)		$768,174	$768,982	$769,086

* 'pooled analysis' in the submitter's report combines all NTRK fusion cancers together for the larotrectinib arm and takes a weighted average of the best-supportive care comparator arms for eleven cancer sites (NSCLC, adult STS, pediatric STS, thyroid, colorectal, salivary gland, biliary, melanoma, secretory breast, appendix, and pancreatic cancer) to create a single comparator arm.

The EGP identified several limitations to the submitter's analyses. These included:

- 'Pooled' analysis violates the following modelling and statistical assumptions:
    - The 'average' ICUR across multiple indications and patient populations with different comparators, across which the treatment may be differentially effective, and for which different reimbursement decision can be made is difficult to interpret. A decision on cost-effectiveness based on an 'average' ICUR may mask the population of patients for whom the agent may be cost effective or populations where the agent may not be cost-effective.
    - The population composition of the 'pooled' PFS and OS curves is changing with time as patients with a tumor type with poor prognosis will leave the 'at-risk' population earlier due to faster rates of progression or death. This effect cannot be separated from the possibility of different rates of response to treatment across tumor sites. Hence, 'pooled' survival curves violate the assumption of population homogeneity.
    - Similarly, the Markov assumption of homogeneity of the population in a health state is also violated. First, as mentioned above in the survival curve analysis, but also on the 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.
- Insufficient number of tumor-specific analyses: the clinical trials included patients with fourteen different tumor types; however, the submitter only provided models for four tumour types initially. Two additional tumour-specific models were provided by the

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submitter upon request from the EGP. However, the submitter was not able to provide a model for salivary gland tumour, despite this tumor 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 lack of information on the selection of an appropriate comparators in this setting to build a site-specific model. Having provided the abovementioned models, the submitter clarified that a consistent range of cost-effectiveness results is demonstrated and, given the limitations of the data, there is a diminishing value gained with additional models. The submitter indicated that the uncertainties in larotrectinib's economic value are best addressed through real-world evidence generation and performance-based risk-sharing. The EGP is thus unable to comment on the cost-effectiveness of cancers that were not modeled.

- Uncertainty in the short-term larotrectinib survival insufficiently captured: uncertainty in tumour-specific larotrectinib survival curves was not captured in the probabilistic analysis for 15 cycles and hence, in some situations 100% PFS and OS were assumed certain despite very small sample sizes and short follow-up period.

- Appropriateness or representativeness of the comparator survival curves: only one clinical trial or observational study was used to inform the survival curves of each comparator arm. No justification was made for the choice of the trial when more than one trial was available. In some cases, the chosen trial is unlikely to be representative of current Canadian practice and outcomes (e.g., study performed in Japan). Furthermore, none of the trials selected to represent the comparator arm had data specific to patients with the NTRK gene fusion. Given the lack of data on the natural history of the NTRK gene fusion and its prognostic impact across different tumours, it is possible that the subset of patients affected by NTRK fusion have different PFS and OS than other patients in these trials.

- Costs of diagnostic testing underestimated: In most of the tumour-specific models, the costs of diagnostic testing were not considered incremental. This is inconsistent with current Canadian practice as NTRK testing is not routinely tested and its addition to current screening would require additional resources.

- Non-treatment health care costs incompletely accounted for: Because the treatment is predicted to increase life-expectancy, omitting the inclusion of non-treatment health care costs favors larotrectinib.

- Health state utilities for the pre-progression health state do not represent a homogeneous population: As previously mentioned, the patient mix in a single health state varies with time, but this has not been considered in utility values as the submitted analysis uses a weighted average of utility values for responders and non-responders to inform the utility of the pre-progression health state.

- Adverse events occurring only in the first cycle of the analysis: adverse events (associated with utility decrement and costs) are modelled as a proportion of patients in the first cycle only rather than as an exposure over time. This does not account for different durations of follow-up across comparator trials informing the adverse event rates. Furthermore, it does not account for the possibility of higher absolute rates when patients have longer exposure than observed in the trial. Hence, in the submitter's model, adverse event rates are the same for a model horizon of 5 or 10 years.

- Time horizon not always representative of tumor-specific population expected survival: in several cases, the 5-year horizon chosen by the submitter resulted in more than 30% of the

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cohort being still alive at the end of the analysis horizon (e.g., pediatric STS, thyroid) and hence, this is not consistent with a lifetime horizon considering the natural history of the disease in this patient population.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP addressed the submitter's analysis by:

- Extending the time horizon to 20 years or when >99% of the cohort in the larotrectinib arm had progressed to the dead health state.
- Incorporating greater uncertainty in the short-term larotrectinib progression-free and overall survival curves. The uncertainty around the measure was estimated mathematically through a Jeffreys Interval which uses a single point estimate of PFS and OS at 15 months and the original size of the patient group to estimate the uncertainty. Alternative approaches to estimate the uncertainty in the survival curves were considered and all methods resulted in similar 95% confidence intervals with the Jeffreys interval typically being between the estimates provided by the other two methods.
- Including baseline (non-cancer) health care costs using the average cost of health care at the average age of diagnosis for each cancer site. This cost was added to the cost of care for patients in all living health states in both treatment arms.
- Including probabilistic uncertainty for the proportion of patients with adverse events. In its base case, the submitter considered the proportion of patients with adverse events to be certain, i.e., proportions were not varied in the probabilistic analysis. The EGP included uncertainty in the proportion of patients with adverse events using beta distribution in its reanalyses.
- Stratifying the pediatric STS population into 'older' and 'younger' patients to specifically model very young pediatric patients who will have a lower treatment dose and require hospitalization to receive the current VAC regimen
- Incorporating additional costs of testing with several different scenarios representing the diversity of costs which may be incurred across Canadian jurisdictions

However, the EGP could not address some of the limitations, for example regarding the representativeness of trials selected by the manufacturer for the comparator arms, and the health state utility assumptions. Furthermore, even though it would have been appropriate, sequential analysis was not possible given the structural assumptions made by the submitter regarding long-term survival.

*The results of EGP reanalysis are presented in **Table 3***

Among patients with a known NTRK gene fusion, the median incremental cost utility ratio (ICUR) compared to best supportive care was the lowest for colorectal cancer ($169,381 per QALY-gained). For all other indications, the ICUR was greater than $400,000 per QALY-gained. In lung cancer, the ICUR of larotrectinib compared to pembrolizumab plus platinum was $70,619 per QALY-gained. In pediatric STS for which NTRK gene fusions are characteristic of the cancer (congenital infantile fibrosarcoma and congenital mesoblastic nephroma), the ICUR of larotrectinib was $768,174 per QALY-gained. In all cases, uncertainty was notable. For several indications the possibility that larotrectinib resulted in fewer QALYs than the comparator exceeded 3%; in the case of melanoma, larotrectinib resulted in lower QALYs than BSC in 15% of simulations.

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Table 3. Summary of EGP's re-analysis for the incremental costs, quality-adjusted life-years, and cost effectiveness of larotrectinib in patients known to have an NTRK fusion cancer.

Tumor site /Comparator	Incremental cost (95% CI)	Incremental QALY (95% CI)	Probability larotrectinib is clinically dominated*	Median ICUR** (95% CI)	Prob. larotrectinib is preferred at a CE threshold of $100,000 per QALY-gained	Price reduction required to achieve median ICUR <$100,000 per QALY-gained
Colorectal cancer: larotrectinib vs.						
Trifluridine + Tipiracil	$85,725 (22,000 - 174,000)	0.40 (0.09 - 0.73)	0.5%	$214,079 (55,000 - 816,000)	12%	40%
BSC	$77,359 (14,000 - 166,000)	0.45 (0.15 - 0.76)	0.1%	$169,381 (32,800 - 473,000)	21%	30%
Lung cancer: larotrectinib vs.						
Pembro. + platinum	$20,609 (-120,000 - 152,000)	0.38 (-0.03 - 0.80)	3.7%	$70,619 (Cost-saving - Clinically dominated)	63%	None
Nivolumab	$241,169 (99,000 - 371,000)	0.66 (0.30 - 1.02)	0.1%	$368,371 (224,600 - 517,100)	0%	50%
BSC	$304,447 (190,000 - 392,000)	0.74 (0.49 - 0.96)	0%	$416,294 (322,200 - 491,600)	0%	75%
Melanoma: larotrectinib vs.						
BSC	$190,509 (81,000 - 307,000)	0.32 (-0.23 - 0.94)	15.2%	$597,750 (258,000 - Clinically dominated)	0%	70%
Thyroid cancer: larotrectinib vs.						
Lenvatinib	$345,592 (89,000 - 591,000)	0.70 (-0.14 - 1.43)	4.8%	$505,913 (165,500 - Clinically dominated)	1%	45%
BSC	$406,083 (274,000 - 515,000)	0.70 (-0.21 - 1.36)	5.4%	$541,087 (336,000 - Clinically dominated)	0%	75%
Adult STS: larotrectinib vs.						
vs. BSC	$398,988	0.95	0%	$421,888	0%	70%

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Tumor site /Comparator	Incremental cost (95% CI)	Incremental QALY (95% CI)	Probability larotrectinib is clinically dominated*	Median ICUR** (95% CI)	Prob. larotrectinib is preferred at a CE threshold of $100,000 per QALY-gained	Price reduction required to achieve median ICUR <$100,000 per QALY-gained
	(313,000 - 485,000)	(0.69 - 1.21)		(375,400 - 490,000)		
Pediatric STS (Full dose scenario): larotrectinib vs.						
VAC	$1,220,570 (557,000 - 2,148,000)	0.91 (-0.12 - 2.08)	3.9%	$1,295,244 (564,930 - Clinically dominated)	0%	>90%
Pediatric STS (Half dose scenario, patients <2 yrs): **larotrectinib vs.**						
VAC	$731,685 (291,323 - 1,352,978)	0.91 (-0.12 - 2.09)	3.9%	$768,174 (320,308 - Clinically dominated)	0%	78%

* Probability that larotrectinib has a lower average QALYs than the comparator

** Results from 5000 simulations were ranked in the following order: Cost-saving (larotrectinib increased QALYs and decreased costs), Standard ICURs in increasing order (larotrectinib increased QALYs and increased costs), Clinically dominated (larotrectinib decreased QALYs). The median ICUR (50th percentile) and the empiric 95% confidence interval are presented.

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Incorporating the cost of testing greatly increased the ICURs for most indications and comparator sets (**Table *4***). Furthermore, the analysis was highly dependant on the frequency of NTRK gene fusion. As the frequency of NTRK gene fusion is uncertain and variable across tumor types, the EGP performed two scenarios for each indication based on low and high values reported in the literature and the submitter's submission. In the high frequency scenario, the lowest ICUR was again in CRC when larotrectinib was compared to BSC ($256,653 per QALY-gained). The ICUR exceeded $400,000 per QALY-gained for all other indications and comparisons. In the low frequency scenario, in which the frequency of mutation was generally consistent with the manufacturer's base case input except in the case of thyroid (for which the higher frequency rate was closer to the manufacturer's base case mutation frequency), the indication of adult STS had the lowest ICUR of $580,830 per QALY-gained compared to BSC. In relatively common cancers, such as colorectal cancer, lung cancer, and melanoma, the ICUR of testing for NTRK gene fusion followed by larotrectinib treatment has an ICUR exceeding $900,000 per QALY-gained. This contrasts the analysis excluding the costs of testing which identified colorectal cancer and lung cancer as having among the lower ICURs for at least one comparator option.

Price reduction necessary to achieve cost-effectiveness

*To estimate an overall percent price reduction needed to achieve an ICUR of $100,000 per QALY-gained in patients known to have NTRK gene fusions, the EGP took a weighted average of the indication specific necessary price reduction with weights based on the expected number of patients with each indication. This identified an average necessary price reduction of 55% when larotrectinib is compared to BSC (**Table 3**). The price reduction is lower than the necessary price reductions for all of the individual indications except CRC because this indication is so common it strongly influences the average. Excluding CRC, the price reduction required to achieve an ICUR of $100,000 per QALY-gained is 74%.*

Incorporating the cost of testing, a minimum price reduction of 75% is necessary to achieve an ICUR of $100,000 per QALY-gained if NTRK fusions are generally more common (always the higher frequency scenario) (**Table *4***). If the frequency of NTRK fusions is less common (closer to the low frequency estimate for each cancer site), then there is no level of price reduction alone such that it is possible for larotrectinib to be cost-effective at a cost-effectiveness threshold of $100,000 per QALY-gained. This is driven by the impact of colorectal cancer, lung cancer, and melanoma which, despite the low frequency of NTRK gene fusion among patients, occur in high overall numbers and in which testing for NTRK gene fusion followed by larotrectinib treatment has an ICUR exceeding $900,000 per QALY-gained. Focusing only on the indications of Radioactive iodine-resistant papillary thyroid cancer, adult STS, and pediatric STS primarily affecting children under the age of 2 (congenital infantile fibrosarcoma and congenital mesoblastic nephroma), a price reduction of 85% results in the testing and treatment of NTRK gene fusions with larotrectinib having an ICUR of $100,000 per QALY-gained.

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Table 4. Summary of EGP's re-analysis for the incremental costs, quality-adjusted life-years, and cost-effectiveness of larotrectinib incorporating the costs of identifying patients using NGS at an incremental cost of $750 at two levels of NTRK fusion cancer frequency among tested individuals.

Tumor site /Comparator	Low mutation frequency			High mutation frequency		
	Testing cost per patient identified	Median ICUR** (95% CI)	Price reduction required to achieve median ICUR <$100,000 per QALY-gained	Testing cost per patient identified	Median ICUR** (95% CI)	Price reduction required to achieve median ICUR <$100,000 per QALY-gained
Colorectal		NTRK frequency: 0.2%			NTRK frequency: 2%	
Trifluridine/ Tipiracil	$375,000	$1,156,944 (642,864 - 5,071,494)	Not achievable	$37,500	$310,285 (129,433 - 1,222,876)	75%
BSC	$375,000	$1,010,149 (603,768 - 2,916,342)	Not achievable	$37,500	$256,653 (106,753 - 687,561)	65%
Lung cancer		NTRK frequency: 0.2%			NTRK frequency: 2%	
Pembro. +platinum	$375,000	$983,130 (594,793 - Clinically dominated)	>95%	$37,500	$165,771 (Cost saving - Clinically dominated)	8%
Nivolumab	$375,000	$920,177 (690,972 - 1,682,306)	Not achievable	$37,500	$424,569 (290,681 - 626,091)	58%
BSC	$375,000	$918,383 (777,552 - 1,213,904)	Not achievable	$37,500	$466,665 (378,134 - 557,719)	85%
Melanoma		NTRK frequency: 0.2%			NTRK frequency: 2%	
BSC	$375,000	$1,796,431 (687,442 - Clinically dominated)	Not achievable	$37,500	$716,851 (305,571 - Clinically dominated)	85%
Thyroid		NTRK frequency: 2.3%			NTRK frequency: 10%	
Lenvatinib	32,609	$555,857 (204,618 - Clinically dominated)	50%	7,500	$519,865 (178,759 - Clinically dominated)	45%

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Tumor site /Comparator	Low mutation frequency			High mutation frequency		
	Testing cost per patient identified	Median ICUR** (95% CI)	Price reduction required to achieve median ICUR <$100,000 per QALY-gained	Testing cost per patient identified	Median ICUR** (95% CI)	Price reduction required to achieve median ICUR <$100,000 per QALY-gained
BSC	32,609	$586,167 (362,115 - Clinically dominated)	84%	7,500	$551,949 (343,306 - Clinically dominated)	78%
Adult STS		NTRK frequency: 0.5%			NTRK frequency: 2%	
BSC	150,000	$580,830 (507,390 - 697,963)	>95%	37,500	$461,363 (409,288 - 540,989)	80%
Pediatric STS (Full dose scenario, patients ≥ 2 yrs)		NTRK frequency: 0.5%			NTRK frequency: 2%	
VAC	150,000	$1,470,870 (664,101 - Clinically dominated)	Not achievable	37,500	$1,341,143 (589,047 - Clinically dominated)	>95%
Pediatric STS (Half dose scenario, patients <2 yrs)		NTRK frequency: 90%			NTRK frequency: 100%	
VAC	833	$769,086 (321,326 - Clinically dominated)	78%	750	$768,982 (321,248 - Clinically dominated)	78%

** Results from 5000 simulations were ranked in the following order: Cost-saving (larotrectinib increased QALYs and decreased costs), Standard ICURs in increasing order (larotrectinib increased QALYs and increased costs), Clinically dominated (larotrectinib decreased QALYs). The median ICUR (50th percentile) and the empiric 95% confidence interval are presented.

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1.5 Evaluation of Submitted Budget Impact Analysis

The manufacturer submitted a 3-year budget impact analysis from the perspective of the Ontario Drug Benefit (ODB) program to estimate the budget impact of drug costs alone or in combination wit the cost of testing. The budget impact report assumed a duration of larotrectinib therapy of 24 months (or median PFS when median PFS was less than 2 years). As a result, the 3-year BIA only included treatment costs for 5 months for colorectal cancer and NSCLC and two years in other cases. Further, the budget impact analysis assumed incremental diagnostic costs only for patients with NSCLC, CRC, and "Other". Given that these assumptions on the length of treatment and number of patients to be tested did not align with the input from the CGP, the EGP used the pharmacoeconomic model to determine the fraction of patients on larotrectinib and the comparator treatment over the first three years. Undiscounted costs of treatment, for both larotrectinib and each comparator, over the first three years were taken directly from the pharmacoeconomic model since the duration of therapy did not align with the manufacturer's assumptions in the BIA.

Factors that affected the budget impact analysis included whether testing costs were included for all cancer sites, duration of larotrectinib therapy, the frequency of testing, and the frequency of NTRK gene fusion.

EGP reanalysis of the budget impact identified a greater 3-year budget impact, compared to the BIA submitted, by calculating the expected annual larotrectinib cost using the health economic model's estimates of the proportion of patients in the progression-free survival health state and by including the incremental costs of adding NTRK gene fusion to standard genetic panels for all cancers. The EGP analysis identified high uncertainty in the budget impact attributable to the uncertainty in treatment effectiveness (duration in progression-free survival) and the frequency of NTRK gene fusion (**Table *5***).

In total, the EGP estimates that if 50% of patients with CRC, thyroid, melanoma, and sarcoma (both adult and pediatric sarcomas affecting patients over 2-years of age), 75% of NSCLC patients, and 100% of patients with congenital infantile fibrosarcoma (CIFS) and congenital mesoblastic nephroma are screened for NTRK gene fusion, the incremental budget impact of drug cost alone is estimated to be between $41.7 and $345.0 million depending on mutation frequency; including the cost of testing increases the 3-year budget impact to between $112.8 million and $416.1 million.

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Table 5. EGPs 3-year net budget impact of NGS testing and larotrectinib treatment across Canada varying the frequency of NTRK gene fusion and the rate of genetic testing uptake.

	Tumor Incidence	Low frequency of NTRK gene fusion				High frequency of NTRK gene fusion			
		Freq.	Fraction of incident population tested using NGS			*Freq.*	Fraction of incident population tested using NGS		
			100%	*75%*	*50%*		*100%*	*75%*	*50%*
Drug cost only									
Colorectal cancer	26,800	0.2%	$11,432,237	$8,574,178	$5,716,119	2%	$114,322,375	$85,741,781	$57,161,187
Non-squamous NSCLC	18,300	0.2%	$24,789,515	$18,592,136	$12,394,757	2%	$275,439,052	$206,579,289	$137,719,526
Melanoma	7,200	0.2%	$8,145,760	$6,109,320	$4,072,880	2%	$77,578,662	$58,183,997	$38,789,331
Radioactive iodine-resistant papillary thyroid cancer	530	2.3%	$11,923,698	$8,942,773	$5,961,849	10%	$51,842,165	$38,881,624	$25,921,083
Adult STS	1,130	0.5%	$5,272,482	$3,954,362	$2,636,241	2%	$21,089,928	$15,817,446	$10,544,964
Pediatric STS (>2 years of age)	100	0.5%	$560,351	$420,263	$280,176	2%	$2,241,405	$1,681,054	$1,120,703
Pediatric STS (< 2 years of age)*	10	90%	$4,400,031	$3,300,023	$2,200,015	100%	$4,888,923	$3,666,692	$2,444,461
Including cost of screening									
Colorectal cancer	26,800	0.2%	$71,732,237	$53,799,178	$35,866,119	2%	$174,622,375	$130,966,781	$87,311,187
Non-squamous NSCLC	18,300	0.2%	$65,973,515	$49,480,136	$32,986,757	2%	$316,623,052	$237,467,289	$158,311,526
Melanoma	7,200	0.2%	$24,345,760	$18,259,320	$12,172,880	2%	$93,778,662	$70,333,997	$46,889,331
Radioactive iodine-resistant papillary thyroid cancer	530	2.3%	$13,116,198	$9,837,148	$6,558,099	10%	$53,034,665	$39,775,999	$26,517,333
Adult STS	1,130	0.5%	$7,814,982	$5,861,237	$3,907,491	2%	$23,632,428	$17,724,321	$11,816,214
Pediatric STS (>2 years of age)	100	0.5%	$785,351	$589,013	$392,676	2%	$2,466,405	$1,849,804	$1,233,203
Pediatric STS (< 2 years of age)*	10	90%	$4,422,531	$3,316,898	$2,211,265	100%	$4,911,423	$3,683,567	$2,455,711

* congenital infantile fibrosarcoma (CIFS) and congenital mesoblastic nephroma

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1.6 Conclusions

Based on the available evidence and analysis performed by the EGP, the incremental cost effectiveness of larotrectinib compared to current last line therapy (best supportive care) or compared to current standards of care for patients with NTRK gene fusion cancers exceeds $400,000 per QALY-gained in most indications.

- Although the incremental cost utility ratio is also highly uncertain, it is unlikely that the ICUR is less than $250,000 per QALY-gained for any indication as the lower 95% confidence interval for most ICUR's exceeded this value.
- For specific indications where the comparator therapy is highly expensive the estimated ICUR is lower, e.g., pembrolizumab plus platinum for NSCLC with an ICUR of $70,600 per QALY-gained and CRC where the EGP's ICUR is $169,400 per QALY-gained.
- For indications where the comparator therapy is not highly expensive, the ICUR substantially exceeds $400,000 per QALY-gained, e.g., the ICUR of larotrectinib for pediatric sarcomas for which NTRK fusion is a characteristic feature is $768,200 per QALY-gained.

Main factors that influence ΔE

- The clinical benefit of larotrectinib is highly uncertain. For several indications, the probability that larotrectinib provides negative clinical benefit exceeds 3% as in melanoma where the probability that larotrectinib provides negative clinical benefit is 15%.

Main factors that influence ΔC

- Currently NTRK gene fusion testing is not routine for any specific cancer type outside of research purposes. Testing for NTRK gene fusion by immunohistochemistry continues to be an area of research. Adding NTRK gene fusion testing to current NGS genetic profiles is estimated to cost an incremental $750 for indications where routine genetic panels are performed early in the treatment regimen. For indications where no genetic testing is currently performed (e.g., thyroid cancer, adult sarcoma) and in some provinces without in-house NGS capacity, NTRK testing may cost an additional $3000 per patient screened.
- Incorporating an incremental cost of $750 per screened patient increases the ICUR of larotrectinib substantially.
- If the frequency of NTRK gene fusion is relatively high (2% for most indications and 10% for thyroid cancer), the ICUR of testing and treatment increases in each case by approximately $50,000. If the frequency of NTRK gene fusion is rare (0.2% for most cancer sites and 2.3% for thyroid cancer), the ICUR exceeds $900,000 per QALY gained for CRC, NSCLC, and melanoma.
- EGP estimates that if 50% of patients with CRC, thyroid cancer, melanoma, and adult and pediatric sarcomas affecting patients over 2-years of age, 75% of NSCLC patients, and 100% of patients with congenital infantile fibrosarcoma (CIFS) and congenital mesoblastic nephroma are screened for NTRK gene fusion, the incremental budget impact of drug cost alone is estimated to be between $41.7 and $345.0 million depending on mutation frequency; including the cost of testing increases the 3-year budget impact to between $112.8 million and $416.1 million.

Overall conclusions of the submitted model:

Individual indications have very different cost-effectiveness and budget impact profiles illustrating drivers for these metrics.

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- For example, the incremental cost-utility ratio of larotrectinib compared to best supportive care in colorectal cancer patients known to have NTRK gene fusion is the lowest at $169,381 (95% CI: 32,800 to 473,000) and has the greatest probability of being cost effective at a willingness to pay threshold of $100,000 per QALY-gained (22%). In part this is due to poor prognosis and relatively high cost of the best supportive care alternative. However, if only 0.2% of CRC patients have NTRK gene fusion, which is consistent with the manufacturer's estimated prevalence, then the ICUR incorporating the cost of testing increases to over $1 million per QALY-gained because 500 people require testing to identify one patient with an NTRK gene fusion. The 3-year Canadian budget impact of testing and treating in 50% of incident CRC cases (consistent with the rate of genetic testing in CRC), would be $35.9 million of which only $5.7 million would be drug cost. The ICUR of testing and treating is lower if the mutation is more common (ICUR of $256,700 per QALY-gained if 2% of CRC patients have NTRK gene fusions), but the 3-year budget impact increases to $131 million, $85.7 million of which is incremental drug cost.

Generalizable insights from this analysis indicate that:

- Larotrectinib treatment in patients with known NTRK gene fusion is more likely to be cost effective when the treatment alterative provides a poor prognosis and is costly (e.g., CRC and NSCLC) and not likely to be cost effective in patients with relatively better prognosis (longer survival) and lower cost alternatives (e.g., melanoma, thyroid, pediatric STS).
- Incorporating the incremental cost of screening only moderately increases the ICUR when the mutation is relatively common (e.g., thyroid) and tremendously when the mutation is rare (e.g., in CRC the ICUR without the cost of testing is $169,000 per QALY-gained and with testing exceeds $1 million).
- The budget impact depends on the incidence of the cancer overall, with more common cancers (e.g., CRC, lung cancer, melanoma) resulting in the largest drug-cost and diagnostic testing budget impact.
- There is an explicit trade-off between budget impact and cost-effectiveness of testing and treatment:
    - if the mutation is rare, the budget impact is lower and disproportionately spent on testing but the implementation of testing and treatment is likely to have an incremental cost utility ratio exceeding $900,000 per QALY-gained;
    - if the mutation is more common, the budget impact is greater and driven more-so by the price of treatment (rather than by screening) and the cost utility ratio is lower (but still exceeding $400,000 per QALY gained).
- Price reduction alone is not sufficient in all cases to achieve an ICUR less than $100,000 per QALY-gained:
    - For thyroid cancer and pediatric sarcomas characterized by NTRK gene fusion, both cases where testing has little impact on the cost-effectiveness, a price reduction of 78% achieves an incremental cost effectiveness ratio of $100,000 per QALY-gained.
    - For other cancer sites, a 78% price reduction achieves an ICUR of testing and treatment when the mutation frequency is at least 2%. However, if the mutation frequency is less than 1%, testing for NTRK fusion and treatment with larotrectinib cannot be cost effective with price reduction alone.

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2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

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3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lung, Breast, Gastrointestinal, Pediatric, Sarcoma and Endocrine Clinical Guidance Panels (CGP) and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of larotrectinib (Vitrakvi) for NTRK positive solid tumours. A full assessment of the clinical evidence of larotrectinib (Vitrakvi) for neurotrophic tyrosine receptor kinase (NTRK) positive solid tumours is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR program. The panel members were selected by the pCODR program, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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