CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

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

October 31, 2019

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding larotrectinib (Vitrakvi) for neurotrophic tyrosine receptor kinase (NTRK) positive solid tumours. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding larotrectinib (Vitrakvi) for NTRK positive solid tumours conducted by members of the Lung, Breast, Gastrointestinal, Pediatric, Sarcoma and Endocrine Clinical Guidance Panels (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on larotrectinib (Vitrakvi) for NTRK positive solid tumours, a summary of submitted Provincial Advisory Group Input on larotrectinib (Vitrakvi) for NTRK positive solid tumours, and a summary of submitted Registered Clinician Input on larotrectinib (Vitrakvi) for NTRK positive solid tumours, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

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

Health Canada has issued marketing authorization for the use of larotrectinib for the treatment of adult and pediatric patients with solid tumours that have a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options. The marketing authorization was issued with conditions, pending the results of trials to verify its clinical benefit.

The recommended dose of larotrectinib in adults is 100 mg taken orally, twice daily until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. In pediatric patients dosing is based on body surface area (BSA). The recommended dose of larotrectinib in pediatric patients (1 month to 18 years) is 100 mg/m^2 taken orally, twice daily with a maximum of 100 mg per dose until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR review included three ongoing, open-label, single-arm trials of larotrectinib in adult and pediatric patients with advanced or metastatic solid tumors: a phase I adult dose escalation and expansion trial (study LOXO-TRK-14001), a phase I/II pediatric trial (study LOXO-TRK-15003; SCOUT trial), and a phase II basket trial in adults and adolescents (study LOXO-TRK-15002; NAVIGATE trial).

- LOXO-TRK-14001 is a multicentre, open-label, ongoing (initiated in May 2014) phase I dose escalation and expansion trial in adult patients with an advanced or metastatic solid tumour. The study included adult patients (≥ 18 years of age), with ECOG performance score of 0-2, and locally advanced or metastatic solid tumor that had progressed, was nonresponsive to available therapies, was unfit for standard chemotherapy, or for which no standard or available curative therapy existed. Although NTRK gene fusion status was not among inclusion criteria for the trial, for the integrated analysis informing the main clinical evidence in the CADTH review, only patients with the NTRK positive gene fusion were prospectively selected for inclusion. In the dose escalation phase, patients received increasing dose levels (50 mg daily to 200 mg twice daily) until the occurrence of dose-limiting toxicity (DLT) in cycle 1, or until the maximum tolerated dose (MTD) was reached. Patients in the expansion cohorts were treated at the MTD, or at a dose level deemed by the sponsor to provide significant TRK inhibition. Treatment was continued until progression, unacceptable toxicity, or patient withdrawal. The primary endpoint of the study LOXO-TRK 14001 was the safety of larotrectinib (including dose-limiting toxicity) and identification of the MTD. Secondary endpoints included overall response rate (ORR) and duration of response (DOR).[1,2]

- The LOXO-TRK-15003 (SCOUT) trial is a multicentre, open-label, phase I/II trial in pediatric patients with advanced solid or primary CNS tumours. The trial included infants, children, and adolescents aged 1 month to 21 years with locally advanced or metastatic solid tumours or CNS tumours that had relapsed, progressed, or had inadequate response to available therapies. In phase I dose escalation, patients received larotrectinib in increasing doses according to SimCyp® dose escalation modeling (based on age and body surface area (BSA) in two cohorts and using a BSA-based dose for three additional cohorts. In phase I expansion and phase II, the starting dose of 100 mg twice daily was used based on previous testing in adults. Larotrectinib was administered orally twice daily, based on 28-day cycles. Treatment was continued until progression, unacceptable toxicity, or patient withdrawal.[2-4] Patients received one of five pre-planned doses of larotrectinib or increasing dose levels until the MTD was reached. The primary endpoint of the phase I dose escalation component was the safety of larotrectinib, including dose-limiting toxicity. The anti-tumour activity of larotrectinib was assessed in phase I expansion and phase II through measurement of ORR (per RECIST version 1.1), PFS, OS, and assessment of pain and health-related quality of life (HRQOL).[3]

- The LOXO-TRK-15002 (NAVIGATE) trial is an ongoing open-label, multicentre trial in adolescent and adult patients with advanced cancer harboring an NTRK gene fusion. The trial consisted of nine cohorts of patients with solid tumors harbouring NTRK fusions, including: 1) non-small cell lung cancer, 2) thyroid cancer, 3) sarcoma, 4) colorectal cancer, 5) salivary gland cancer,6) biliary cancer, 7) primary CNS tumor, 8) all other solid tumor types with evaluable but not measurable disease; and 9) patients with an NTRK gene fusion identified in a lab where certification of the lab cannot be confirmed by the Sponsor. The trial included patients with locally-advanced or metastatic solid tumour, with an NTRK gene fusion, who were 12 years of age and older and had an ECOG performance score of 0-3. Patients were required to have received prior standard therapy or, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy. Larotrectinib was administered 100 mg orally in individuals with a body surface area (BSA) ≥1 m^2, or 100 mg/m^2 orally twice daily for children and adolescents with a BSA <1 m^2, twice daily, based on 28-day cycles. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal. The primary endpoint of the trial was ORR, as determined by an independent radiology review committee (IRC) using RECIST (version 1.1) or RANO criteria. Secondary endpoints included: investigator-

assessed ORR, DOR: CBR, PFS, OS, and safety. HRQoL was measured as an explanatory endpoint.[4]

Additional information on the characteristics of the included trials can be found in section 6.3.2.1.

Pooled analyses

The pCODR submission for larotrectinib is based on a pooled analysis of efficacy and safety data from the three trials (LOXO-TRK-14001, SCOUT, and NAVIGATE). The pooled analyses included adult and pediatric patients who were enrolled across the three larotrectinib studies if they met the following criteria:

- documented NTRK gene fusion as determined by local testing;
- non–central nervous system primary tumour with one or more measurable lesions at baseline that could be assessed according to RECIST, version 1.1; and
- received one or more doses of larotrectinib.

Pooled analyses were performed using multiple datasets that were created at three data cut-off dates: 17-July-2017, 19-February-2018 and 30-July-2018 (see section 6 for more details). This pCODR review is mainly focused on the latest dataset that consists of 122 larotrectinib-treated patients with NTRK gene fusions, who had their outcomes assessed by the investigator (Integrated dataset; 30-July-2018 data cut-off). The reported pooled OS analysis is based on the 19-February-2018 data cut-off (Extended Primary Analysis set; n= 73), as the OS results were not available from the Integrated analysis. A summary of the efficacy and safety results from the Integrated pooled analysis are presented in Table 1.1.

Efficacy

ORR: As of the 30-July-2018 data cut-off date, ORR was 81% (95% CI 72%, 88%); 17% of patients achieved a CR and 63% achieved a PR. The median time to response was 1.8 months. At the data cut-off, 84% of responding patients (73% of all patients) remained on treatment or had undergone surgery with curative intent.[5,6]

ORR was consistent across all subgroups based on baseline disease characteristics (ECOG status and metastatic cancer status), and number of prior treatment regimens. However, the subgroup analyses of ORR also indicated that ORR results varied across patient age groups, tumour types, and NTRK gene fusion or major NTRK isoforms (See section 6; Tables 6.5, 6.6, and 6.7).[5] The submitted pooled efficacy analysis excluded adult and pediatric patients who had primary CNS tumours. However, the efficacy of larotrectinib in patients with CNS tumours was analyzed separately. In the subgroup of patients with primary CNS tumours (n= 18), ORR was estimated to be 36% (95% CI 13%, 65%); with CR in 14%, PR in 21%, and stable disease in 64% of the patients.[7]

DoR: As of the 30-July-2018 data cut-off date, the median duration of response had not been reached. The percentage of patients with an ongoing response was 88% at 6 months, and 75% at 12 months from the start of response.[5,6]

PFS: At the 30-July-2018 data cut-off date, after a 19.6 months median duration of follow-up, the median PFS was 28.3 months (95% CI 9.9, not estimable). In their report, the Submitter acknowledged that this estimate was "not statistically stable due to a low number of progression events, as evidenced by the wide confidence interval".[5]

In the feedback received from the Sponsor on the initial pERC recommendation, progression-free survival ratio (PFSr), defined as the ratio at the PFS under line +2 (PFS2) divided by the PFS at line +1 (PFS1), was considered as a "direct intra-patient evaluation

of treatment benefit". Based on the Sponsor's feedback, a PFS2/PFS1 ratio >1.3 would be indicative of a clinically meaningful treatment effect.[8] It was reported in the feedback document that, although PFS was ongoing for many patients treated with larotrectinib in the extended primary analysis set (n=73), 65% of these patients had attained a PFSr ≥ 1.3.[9]

OS: The OS results are not available from the Integrated analysis. In an earlier analysis performed at the 19-February-2018 data cut-off (Extended Primary dataset; n=73), 86% of patients were alive and 14% had died. After a median follow-up of 14.8 months, the median OS had not been reached. At 12 months, the probability of survival was estimated to be 90%.[5]

Quality of Life

Health-related quality of life (HRQoL) and health utilities were exploratory endpoints in the NAVIGATE and SCOUT trials. Patient-reported outcomes were not measured in the LOXO-TRK 14001 trial.

As of 30-July 2018 data cut-off date, 57 patients had completed questionnaires at baseline and at least one post-baseline follow up visit :40 adult patients for EORTC QLQ-C30/EQ-5D-5L and 17 pediatric patients ≥2 years of age for PedsQL.[10]

EORTC QLQ-C30: Of the 40 adult patients who completed EORTC QLQ-C30 questionnaire, 70% had an improvement in global health scores, with 60% reporting improvements that reached or exceeded the MID of 10 points. Among evaluable patients, 41% had an improvement in EORTC QLQ-C30 global health score that lasted for at least two consecutive cycles. EORTC QLQ-C30 global health score improvements were reported for all tumor types.[10]

EQ-5D-5L: Of the 40 adult patients who completed EQ-5D-5L questionnaire, 73% had and improvement in VAS health score, with 60% reporting a post-baseline score that reached or exceeded the MID of 10 points. Among evaluable patients, 51% had an improvement in VAS health score that lasted for at least two consecutive cycles.[10]

PedsQL-Core: Of the 17 pediatric patients who completed PedsQL-Core questionnaire, 88% had improvement in PedsQL total scores, with 76% reporting a best post-baseline score that reached or exceeded the MID of 4.5 points. Among evaluable patients, 65% reported improvements that lasted for at least two consecutive cycles. PedQL total score improvements were observed across tumor types.[10]

Harms outcomes

As of the 30-July-2018 data cut-off date, a total of 207 patients were included in the safety analysis dataset. The majority of the reported adverse events (AEs) were grade 1 or 2. Treatment-related Grade 3 or 4 AEs occurred in less than 5% of patients. The most common Grade 3/4 AEs included anemia, increase in liver enzyme (ALT and AST) levels, and nausea. Eleven out of the 122 patients (9%) in the Integrated analysis set required dose reductions due to AEs, and all maintained tumour regression on a reduced dose.[5,6] Two patients discontinued larotrectinib due to an AE.[11]

Table 1.1 : Highlights of Key Outcomes from the pooled analyses of the NTRK trials (LOXO-TRK-14001, 15002, and 15003)

	Integrated analysis (N=122)†
Efficacy	
Primary Endpoint	

	Integrated analysis (N=122)†		
Primary Efficacy Endpoint			
ORR, % (95% CI)	81 (72, 88)		
Key Secondary Efficacy Endpoints			
TTR [months], median	1.8		
DOR[months], median (range)	NE (NE, NE)		
PFS [months], median (95% CI)	28.3 (9.9, NE)		
OS [months], median (95% CI)	NE (NE, NE)		
12-month OS rate, % (95% CI)	90% (NA, NA)††		
HRQoL	**HRQoL evaluable patients**		
	EORTC QLQ-C30 (N= 40)	EQ-5D-5L (N=40)	PedsQL-Core (N=17)
Patients with best baseline score at or above MID improvement, n (%)	24 (60)	24 (60)	13 (76)
Safety Endpoints			
Treatment-related Grade 3/4 AEs	< 5%¥		
Dose reductions due to AEs	11 (9%)†		
Withdrawal due to AEs	2 (<2%)†		

AEs = adverse events**; CI** = confidence interval; **DOR** = duration of response; **HRQoL** = health-related quality of life; **MID** = minimally important difference; **NA**= not available; **NE**= not estimable; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression-free survival; **TTR** = time to response
† 30-July-2018 data cut-off (Integrated dataset; n=122)
†† 19-February-2018 data cut-off (Extended Primary dataset; n=73)
¥ 30-July-2018 data cut-off (Safety dataset; n=207)

Limitations of the submitted pooled analysis:

Focus on molecular profiling

NTRK gene fusions can occur in various tumour types with different natural histories. The primary objective of the included single arm trials and that of the submitted integrated analysis was not to determine the effect of the drug separately in each tumour type. The treatment effect was rather estimated irrespective of histological tumour type. In other words, an assumption was made by the investigators that the presence of a NTRK gene fusion was sufficient to evaluate the effect of larotrectinib in all relevant tumour types.

Scarcity of historical data

The Submitter acknowledged that there was no literature that demonstrated the impact of NTRK gene fusion proteins on patients' outcomes across tumour types.[5] An independent literature search that was conducted by the pCODR review team was also unable to find studies with acceptable methodological quality that investigated the effects of current standard of care in NTRK positive solid tumours (see section 7). NTRK gene fusions are rare and the natural history of the disease has not been well characterized to date.

In addition, there is a lack of data on comparative efficacy and safety for tumor types that have relevant comparators available. VOYAGER-1 is an ongoing retrospective cohort study that uses secondary data to study the patient characteristics and clinical outcomes in cancer patients with NTRK gene fusion and those in cancer patients without NTRK mutations who received current standard of care in a real-world setting (see section 6.4 for more details). However, as the study is ongoing, outcome results are not currently available.[5]

Heterogeneity in design elements of studies included in the pooled analysis

Interpretation of pooled analysis results remain difficult in the presence of between-study heterogeneity:

i. Different phased studies: Given the rare nature of NTRK fusion positive solid tumors and methodological challenges, the Submitter rationalized that the conduct of a randomized trial was not feasible.[2,5] Therefore, the submitted data was pooled from three single arm trials: a phase I adult trial (LOXO-TRK 14001), a phase I/II pediatric trial (SCOUT), and a phase II basket trial (NAVIGATE) in adults and adolescents. The phase II part of the SCOUT trial, investigating long-term safety and efficacy of larotrectinib in pediatric patients is ongoing and results are yet to be published.

ii. Different primary outcomes: The primary objective of the dose escalation phases of the LOXO-TRK 14001 and SCOUT studies was to determine the safety and tolerability of larotrectinib, while the primary objective of the NAVIGATE trial was to determine the efficacy of larotrectinib by measuring the best overall response rate. The dose expansion cohorts included in the LOXO-TRK 14001 and SCOUT phase I trials were powered to detect a 30% or larger improvements in ORR, as their secondary study objective.

iii. Different requirements for outcome measurement: In the LOXO-TRK 14001 and SCOUT trials, ORR was assessed by the investigator using RECIST (version 1.1) or RANO criteria, as appropriate to tumor type; whereas in the NAVIGATE trial, ORR was determined by an independent radiology review committee using RECIST (version 1.1) or RANO criteria.

iv. Different eligibility criteria: As mentioned earlier in this section LOXO-TRK 14001 included adult patients, SCOUT included pediatric and NAVIGATE enrolled adults and adolescent patients. In addition, the presence of a confirmed NTRK fusion was mandated before enrollment in the NAVIGATE trial; while NTRK positive status was not a requirement for eligibility in the LOXO-TRK 14001 and SCOUT trials. TRK gene fusions were rather identified prospectively in the two latter trials. These sources of heterogeneity in the patient selection criteria may introduce bias to the results of the pooled analysis.

Uncertainty around the pooled analysis results

The following limitations should be considered when interpreting the pooled analysis results:

i. Pooled estimates of response versus survival outcomes: Due to the small sample size, there is uncertainty regarding the magnitude of the treatment effect of larotrectinib in any one histologic subtype of solid tumors with an activating NTRK rearrangement. The Clinical Guidance panel agreed that the pooled ORR estimate for treatment effect was generalizable to all of the subgroups. However, pooling data across tumour types may lead to inflated type I error if the treatment effect is heterogenous across different tumour types.[12] Subgroup analyses of data from the three larotrectinib trial (integrated analysis; n=122) indicated that ORR results varied across tumour types. The reported ORR benefit ranged from 100% in thyroid cancer, gastrointestinal stromal tumor (GIST), and cellular congenital mesoblastic nephroma (CMN) down to 0% in appendix, pancreas and breast cancers, and cholangiocarcinoma (see Table 6.6 for more details). Additionally, imbalanced and small sample sizes for each tumour type could lead to inefficient tumour subgroup analyses, due to lack of statistical power. In the above-mentioned subgroup analysis, there was one patient enrolled in each of appendix, breast CMN and pancreas tumour subgroups.

   Pooling data on survival outcomes (i.e., PFS and OS) could be even more problematic, if there is a variability in the PFS or OS across different tumour types. This is because traditional survival analysis methods such as Kaplan-Meier (KM) curves rely on the assumption that a single survival distribution can be used to estimate the survival of all study participants.

Novel methodological approaches have been proposed to improve the design and analysis of single-arm basket trials and account for potential heterogeneity of response rates across various tumour types. Limited information was available on the use of such methodology in the current review but was deemed non-disclosable by the submitter.[12-15]

ii. Ongoing nature of the included trials: All three larotrectinib trials are ongoing. The LOXO-TRK-14001 trial has stopped enrollment in 2017; however, NAVIGATE and SCOUT are still enrolling patients. Therefore, the results of the pooled analysis are subject to change as more data becomes available.

iii. Risk of selection and immortal time biases: In the NAVIGATE trial, patients who did not have any radiological disease assessments after the initiation of larotrectinib would be replaced by new patients who had a documented disease assessment.[4] It is not clear if the same criterion was used in the LOXO-TRK 14001 and SCOUT trials. Detailed patient disposition data is not available for the pooled integrated analysis. However, based on the CONSORT flow diagram for the Extended Primary analysis (n=73; 19-February-2018 data cut-off), of the first 105 consecutively enrolled and treated patients (across all three trials, 20 patients were excluded from efficacy analysis due to insufficient follow-up to allow Independent Review Committee assessment; six patients were excluded because they did not have a RECIST measurable disease at enrolment; and six additional patients were excluded due to primary central nervous system (CNS) tumors.[5] It is however not clear how many of these patients were replaced. Exclusion of patients with no disease assessment may have introduced bias by selecting patients who had a better compliance. In addition, patients must survive until the first disease assessment visit to have a radiological disease assessment (immortal time bias).

iv. Uncertainty around quality of life data: In addition to the uncertainty in determining the magnitude of effect using pooled data from such a heterogenous population, the number of patients with available HRQoL data is low. The Methods team therefore agree that the HRQoL results are exploratory and should be interpreted with caution.

<u>The use of PFS ratio (PFSr) as an indicator of clinical efficacy</u>

PFSr, also referred to in the literature as the growth modulation index,[16-18] is defined as the ratio of PFS on the last line of therapy (larotrectinib, in the case of the current pCODR review) to the PFS on the most recent prior line of therapy.

In the feedback received from the Sponsor on the initial pERC recommendation, 65% of the larotrectinib-treated patients in the extended primary analysis dataset were reported to have a PFSr equal to or greater than 1.3 (a threshold proposed by Von Hoff et al.[17] as a sign of drug activity). The Sponsor suggested that the PFSr comparison would help address pERC's concerns of heterogeneity of tumour type.[5]

The Methods team acknowledges that PFSr provides an intra-patients drug activity comparison between two consecutive lines of therapy in order to eliminate heterogeneity (between-patient variability). However, the following methodological limitations should be considered when interpreting the PFSr results reported for the pooled analysis of the larotrectinib trials:

i. The Analysis of PFSr was not specified as a clinical endpoint in the included larotrectinib study protocols but was added as an exploratory, post-hoc analysis to support the primary clinical efficacy findings.

ii. All patients included in the larotrectinib trials (and in the pooled analyses) received their prior lines of therapy before enrollment in the study. As a result, data on PFS1 was most likely collected retrospectively. No information was provided in the study

reports on the data collection procedures and missing data. It is not clear if the timing and frequency of disease assessment were consistent between larotrectinib therapy and the previous line of treatment; and if data on PFS1 was available for all enrolled patients. Overall the risks of ascertainment and attrition biases could not be ruled out.

iii. The methods team was unable to identify any studies that validated PFSr with other measures of clinical benefit (e.g., overall survival) in studies of drugs targeting NTRK gene fusions. Another methodological issue inherent to PFSr is that the use of this indicator to assess clinical benefit is dependent on the correlation between PFS1 and PFS2. For example, a patient with a good response to both larotrectinib and their previous line of therapy would attain a lower PFSr.[19,20]

Factors limiting the external validity of the pooled analysis

Other potential limitations of the pooled analysis include:

i. The larotrectinib trials included patients with NTRK+ solid tumours regardless of their tumour type. However, not all solid tumor types were represented in the studies.

ii. The pooled analysis excluded patients with primary CNS tumours.

iii. The eligibility criteria for the three larotrectinib trials did not restrict the number of previous lines of systematic therapy.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

The patient input for 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 was provided through a collaboration of seven patient groups. The participating groups included:

- Canadian Cancer Survivor Network
- Colorectal Cancer Canada
- Lung Cancer Canada
- Neuroblastoma Canada
- Ontario Parents Advocating for Children with Cancer
- Sarcoma Cancer Foundation Canada
- Thyroid Cancer Canada

From a patient's perspective, the presence of a specific genetic tumour biomarker (rather than the site at which the cancer originates) is of paramount importance and unites the various disease sites containing the genetic mutation. Patient respondents have noted that personalized medicines have changed the outlook for cancer patients who have actionable driver mutations. The patient groups in this submission noted that diagnostic testing for the NTRK gene fusion is currently not available or funded in Canada. With the increasing importance of genomic profile testing and personalized medicine, this form of testing is needed. All patient respondents in this submission have genomic testing showed they had the NTRK gene. The patient respondents all have accessed previous therapies for the treatment of their respective cancers and had varying symptoms affecting their daily life.

Patient respondents would expect improved outcomes of larotrectinib to include: improved symptoms, including reduction in pain, increase in mobility, and ease of breath;

better survival rates; better quality of life while effectively controlling their disease and easier form of treatment modality. Patient respondents reported the following treatment-induced side effects with larotrectinib: elevated ALT/AST levels, tinnitus, swollen ankles, withdrawal-like symptoms, overstimulation, fatigue, sensitivity to light, and flu-like symptoms – all of which were considered by respondents to be tolerable and relatively minor. According to the patient respondents, this treatment has delivered a clinically meaningful response in their cancer. Their disease has either resolved completely, significantly or to a great extent, while managing to maintain a high level of quality of life. For those patients who were experiencing cancer-induced symptoms prior to starting Larotrectinib, respondents reported a significant improvement in those symptoms after starting the therapy. Additionally, patient respondents appreciate an easily administered oral therapy in the comfort of their homes.

Please see Section 3 for a summary of specific input received from the patient advocacy groups.

Provincial Advisory Group (PAG) Input

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Place in therapy for larotrectinib

Economic factors:

- Additional health care resources may be required to monitor and treat toxicities
- Number of patients requiring and access to NTRK gene fusion testing

Please see Section 4 for a summary of specific input received from PAG.

Registered Clinician Input

Five clinician inputs were received for the pCODR review of larotrectinib for solid tumours harbouring a NTRK gene fusion. There was one single clinician input, and four joint clinician inputs comprising of 26 oncologists and one pharmacist from the following groups: Colorectal Cancer Canada (CCC; 11 clinicians), the Pediatric Oncology Group of Ontario (POGO; five clinicians), Lung Cancer Canada (LCC; seven clinicians), and Cancer Care Ontario (CCO; three clinicians and one pharmacist). The single clinician input provided input in regard to thyroid, lung, and head and neck cancers. In total, input was received from 27 oncologists and one pharmacist.

All clinicians agreed that patients eligible for larotrectinib would need to present with solid tumours harbouring the NTRK gene fusion. Ideally identification of the NTRK gene fusion would occur during diagnosis of the patient's tumour, or during testing for other mutations. While identification of the NTRK gene fusion is a requirement for patients to

receive larotrectinib, it was identified that there is no routine testing for NTRK currently available, and that testing is not funded. However, a number of tests to identify the NTRK gene fusion were stated, including immunohistochemistry, fluorescent in situ hybridization (FISH), nanostring technologies, next generation sequencing, biopsy or fine needle aspiration cytology (FNAC). None of the clinicians had any experience using larotrectinib, as the clinical trials for the drug were not open in Canada. However, compared to other therapies, such as cytotoxic chemotherapy, larotrectinib was stated to show greater efficacy and a favourable toxicity profile. According to the clinicians providing input, the use of larotrectinib in a specific line of therapy was dependent on the type of cancer being considered.

It was stated in the joint input from the clinicians from CCO that there was not sufficient evidence to identify an unmet need for breast cancer patients at this time. Therefore, larotrectinib was given a low priority by CCO for patients with breast cancer. Alternatively, POGO, LCC, CCO and the single clinician stated that larotrectinib would be useful to patients as it is tolerable, easy to administer as it is an orally administered therapy, and efficacious.

Please see Section 5 for a summary of specific input received registered clinicians.

Summary of Supplemental Questions

The following supplemental question was identified during the development of the review protocol as relevant to the pCODR review of larotrectinib (Vitrakvi) for NTRK positive solid tumours:

1. Prognostic relevance of the NTRK fusion protein in patients with solid tumours

   The literature search did not identify any relevant information that spoke directly to the prognostic relevance of the NTRK fusion protein on various types of cancers. The literature search resulted in seven primary full-text articles, one abstract, and an additional article identified through a reference list. In general, the identified literature reported that the occurrence of the NTRK gene fusion is low although it seems to be more prevalent among less common cancers, such as those presenting in the CNS, and less prevalent among more common cancer types, such as lung cancers. Patient characteristics of those carrying the NTRK gene fusion were found to vary in age, sex, and various relevant diagnostic categories. Two publications commented on the co-occurrence of targetable mutations alongside the NTRK gene fusion, such as PD-L1. While the literature search indicated some potential patterns across patients with presence of an NTRK gene fusion, they could not indicate how the factors affect the prognosis of patients and outcomes. For example, it is unclear how co-existing gene mutations will affect the prognosis of a patient; however, Gatalica et al.[21] stated that with the presence of multiple oncogenic drivers, opportunities for combination therapies may present themselves in the future. In addition, given the wide range of patients that the NTRK gene fusion is detected among, it is not clear which patients may be more likely to have an NTRK gene fusion. While some characteristics of patients with NTRK gene fusions were analyzed, it is unclear how these characteristics and presence of the gene fusion will affect patient's disease prognosis. A review article by Chetty et al.[22] acknowledged that while the gene fusions are the main mechanism by which the oncogenic potential of the NTRK1-3 genes are unleashed, the mechanisms by which the NTRK mutations result in carcinogenesis and progression of a patients' cancer are unknown. Overall, while the identified literatures generally agreed that the NTRK gene fusion is an oncogenic driver in various cancers, the literature search did not identify any relevant data to directly indicate how the presence of the gene mutation affects a patient's prognosis.

See section 7.1 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team identified relevant literature related to testing for neurotrophic receptor tyrosine kinase (NRTK) gene fusion.

See section 8.1 for more information.

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 1.2: Assessment of generalizability of evidence for larotrectinib for patients with solid tumours harbouring an NTRK gene fusion.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>Histological tumour type</td><td>The larotrectinib trials included patients with NTRK+ solid tumours regardless of their tumour type.

The following tumour types were recorded in the study:
– Infantile fibrosarcoma
– Soft tissue sarcoma
– Thyroid
– Salivary gland
– Melanoma
– Breast
– Appendix
– Lung
– GIST
– Colon
– Pancreas
– Cholangiosarcoma
– Congenital mesoblastic nephroma
– Unknown primary tumours
– Bone sarcoma</td><td>Are the study (i.e., pooled analysis) results applicable to all of the NTRK+ tumour included in the larotrectinib trials?

Are the study results applicable to all NTRK+ solid tumours?</td><td>Although some variation was observed in response rates within the subgroup analysis by tumour type, from a histology-agnostic, biomarker-driven perspective, the CGP agreed that the overall pooled analysis results are generalizable to all patients in the pooled analysis regardless of tumor-type and all patients with advanced solid tumors harbouring an NTRK fusion.</td></tr>
<tr><td>Co-mutations</td><td>The larotrectinib trials included in the submitted pooled analysis focused in the presence of documented NTRK gene fusions (determined by local testing).</td><td>Are the study results applicable to NTRK+ patients with other oncogenic co-mutations?</td><td>The results are generalizable to cancers with NTRK1, NTRK2 and NTRK3 gene fusions.</td></tr>
<tr><td>Line of therapy</td><td>The eligibility criteria for the three larotrectinib trials did not restrict the number of previous lines of systematic therapy.
<table><tr><th># previous systemic therapies N (%)</th><th>Integrated analysis (n=122)</th></tr><tr><td>0-1</td><td>66 (54)</td></tr><tr><td>2</td><td>25 (20)</td></tr><tr><td>≥3</td><td>31 (25)</td></tr></table></td><td>Are the trial results applicable to the Canadian practice?</td><td>Yes, there is no clinical rationale to suggest that the trial results would not be applicable to Canadian practice.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Primary CNS tumours</td><td>The pooled analysis excluded patients with primary CNS tumours. However, a separate analysis was conducted to evaluate the efficacy of larotrectinib in 24 patients with CNS tumours (18 primary and 6 non-primary) who had been enrolled in the included larotrectinib trials.
In patients with primary CNS tumours, the ORR was 36% (95% CI 13%, 65%), compared with 81% (95% CI 72%, 88%) in the pooled analysis (integrated analysis set)</td><td>Are the study results applicable to NTRK+ patients with primary CNS tumours?</td><td>Yes, in the opinion of the CGP, the study results are applicable to NTRK+ patients with primary CNS tumours.</td></tr>
<tr><td></td><td>Performance Status</td><td>The inclusion criteria across the three pooled trials required that patients have:
ECOG PS ≤ 2 (LOXO-TRK-14001)
Karnofsky (for patients aged ≥ 16 years) or Lansky (for patients aged <16 years) performance score of at least 50 (SCOUT)
ECOG PS ≤ 3, or Karnofsky performance score of at least 50 for patients with CNS tumours (NAVIGATE)
<table><tr><th>ECOG PS</th><th>Primary Analysis</th><th>ePAS</th><th>Integrated Analysis</th></tr><tr><td>0</td><td>24 (44%)</td><td>33 (45%)</td><td>59 (47%)</td></tr><tr><td>1</td><td>27 (49%)</td><td>33 (45%)</td><td>53 (43%)</td></tr><tr><td>2</td><td>4 (7%)</td><td>7 (10%)</td><td>12 (10%)</td></tr></table></td><td>Are the overall trial results generalizable to patients with poorer performance status (i.e., ECOG >2, LPS <40%, and KPS <50%).</td><td>The trial results are generalizable to patients with ECOG PS 0, 1 or 2 (and their respective performance status equivalence for the pediatric population). While larotrectinib is a tolerable therapy, there is insufficient data to support generalizability to patients with poorer performance status.</td></tr>
<tr><td>Intervention</td><td>Dosing schedule</td><td>The pooled analysis of data from three larotrectinib trials used data from patients who received the recommended dose of:
100 mg (oral dose) twice daily in individuals with BSA ≥1 m^2, or
100 mg/m^2 (oral dose) twice daily for children with a BSA <1 m^2</td><td>Are there other larotrectinib dosing schedules used in Canada for the treatment solid tumours harbouring NTRK gene fusions? If so, are the trial results applicable to the Canadian practice?</td><td>No, there are not other dosing schedules used in Canada.</td></tr>
<tr><td>Comparator</td><td>Post-progression larotrectinib therapy</td><td>At the 31-July-2018 data cut-off date, 15 out of 122 patients (12%) continued larotrectinib beyond progression, while 18 patients (15%) discontinued treatment post-progression.[5]</td><td>Is the study design which allows for treatment beyond progression and the study results applicable to the Canadian practice?</td><td>The CGP agree there is insufficient evidence to support the continued use of larotrectinib beyond disease progression. In Canadian practice, patients would discontinue larotrectinib therapy after progression.</td></tr>
<tr><td>Outcomes</td><td>Appropriateness of Primary and</td><td>The primary endpoint of the pooled analysis ORR determined by IRC.</td><td>Were the primary and secondary outcomes</td><td>Yes, the primary and secondary outcomes were</td></tr>
</table>

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
	Secondary Outcomes	Key secondary endpoints included DOR, PFS and safety. Two of the larotrectinib trials included HRQoL as an exploratory outcome.	appropriate for the trial design?	appropriate for a basket trial design.
Setting	Countries participating in the trial	Five Canadian patients (under 21 years) were enrolled across 3 Canadian sites. : – LOXO-TRK-14001 was conducted in 8 sites in US – LOXO-TRK-15003 (SCOUT trial) is being conduced 20 sites internationally, including 3 sites in Canada. – LOXO-TRK-15002 (NAVIGATE trial) is being conducted 21 sites in US, EU, and Asia	Is there any known difference in the practice pattern between other participating countries and Canada (that might impact the clinical outcomes, or the resources used to achieve the outcomes)?	While there may be small differences in practice patterns, the CGP does not feel these differences would be sufficient to expect the results would not be generalizable to the Canadian patient population.

BSA = body surface area; **DOR** = duration of response; **GIST** = gastrointestinal stromal tumours; **HRQoL** = health-related quality of life; I**RC** = independent radiology review committee (IRC **mg/m^2** = milligram per square meter of body surface; **NTRK =** Neurotrophic Tyrosine Receptor Kinase; **ORR** = -overall response rate; **PFS** = progression-free survival

1.2.4 Interpretation

Burden and Need:

Tumour agnostic indication in solid cancers harbouring an NTRK gene fusion:

Larotrectinib is an oral, selective inhibitor of the TRK family of proteins (TRKA, TRKB and TRKC) that are encoded by the NTRK1, NTRK2 and NTRK3 genes. NTRK gene fusions lead to oncogenic TRK fusion proteins driving constitutive kinase activation. Larotrectinib exerts its activity in solid cancers harbouring an NTRK gene fusion. The frequency of NTRK gene fusions is estimated to be less than 1% across all solid tumours although it is seen more commonly in selected rare tumours including secretory breast cancer, infantile fibrosarcoma, congenital nephroma and mammary analog secretory cancer (MASC) of the salivary gland. (see Background). While NTRK gene fusions are recognized to be oncogenic drivers, there appears to be little data regarding their prognostic impact.

There are currently no approved therapies targeting NTRK gene fusions. The Health Canada indication for larotrectinib (NOC/c granted July 10 2019) is tumour-agnostic; for the treatment of adult and pediatric patients with solid tumours that have an NTRK gene fusion (without a known acquired resistance mutation), are inoperable and/or metastatic and have no satisfactory treatment options.

<u>Selected Disease-site specific Burden and Need considerations:</u>

Pediatric Solid Cancers:
Despite their relative rarity in pediatric oncology, NTRK fusions are pathognomonic of specific, rare cancers including infantile fibrosarcoma (IFS) and cellular congenital mesoblastic nephroma. Several other very rare pediatric cancers, including secretory breast cancer and mammary analog secretory carcinoma of the salivary gland, are also expected to carry NTRK fusions. In addition, there are significant numbers of NTRK fusion cancers among children with papillary thyroid carcinoma, undifferentiated sarcomas, high grade gliomas, inflammatory myofibroblastic tumours and rarely in acute leukemia.

In pediatric advanced solid cancers with an NTRK fusion, the CGP believes there is a significant unmet need for efficacious therapies.

Secretory Breast Cancer:
NTRK gene fusions are quite rare in breast cancer. Currently, there a number of standard therapy options for patients with advanced breast cancer which have considerably improved survival, but many patients will ultimately go on to exhaust available therapies and be left with no suitable therapeutic options.

Secretory breast carcinoma is a very rare histologic subtype of breast cancer that is seen in less than 1% of invasive breast cancer; this subtype is seen in children and adults and is associated with a generally favourable prognosis and a low likelihood of metastases. However, for those patients with advanced, inoperable disease, treatments options are limited. Secretory breast carcinomas are also associated with a >90% prevalence of NTRK gene fusions.[23]

Sarcoma and GIST:
Sarcomas are a relatively rare tumor subtype representing over 100 hundred subtypes. They are often categorized into soft tissue (STS) and bony sarcomas. STS are associated with a less favourable prognosis, and in the adult population, are often not curable.

Limited effective cytotoxic therapies exist for STS, especially in the metastatic setting or upon relapse. STS was the most common histologic subtype included in the larotrectinib pooled analysis (22.9%).

NTRK fusions are also seen in 3-4% of GIST tumours.[2] For GIST tumours with cKIT and PDGFRA mutations, targeted therapies represent the current standard of care. For 10-15% of GIST that are wild-type, there is a significant unmet need for effective therapies.

Thyroid Cancer:
For patients with advanced, inoperable thyroid cancer that has progressed on radioactive iodine therapy, current treatments include small molecule tyrosine kinase inhibitors. As NTRK gene fusions may be identified in 12% of thyroid cancers[24], larotrectinib would address a significant unmet need in this patient population.

Gastrointestinal Cancers:
For patients with advanced colorectal cancer (CRC), there is an unmet need for better therapies in patients with chemorefractory disease (i.e. have progressed on two or more prior lines of therapy). NTRK gene fusions are uncommon in CRC. For patients with non-colorectal GI cancers, particularly pancreatic cancer and cholangiocarcinoma, there is a significant unmet need for better therapies.

Lung Cancer:
Lung cancer remains the most common cancer in Canada. *NTRK* fusions are estimated in up to 1% of NSCLC[23] (as compared to *ALK* fusions in 3-5%, *ROS1* fusions in 1-2%, and *EGFR* mutations in 20%).[25] Systemic treatment options for advanced NSCLC include chemotherapy, immunotherapy, combinations and biomarker-directed targeted therapies, with response rates ranging from 45-60% in those without *ALK*/*EGFR*/*ROS1*/*BRAF*-deranged lung cancer. While these current therapies have improved outcomes for patients with NSCLC, patients will ultimately become refractory and/or intolerant to available therapies; hence there is a need for effective and tolerable therapies in pre-treated patients.

In summary, the CGP believes 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.

Effectiveness:

There are no randomized phase 3 trials evaluating the clinical benefit of larotrectinib in this setting. The CGP recognizes that a randomized, controlled phase 3 trial in this setting would not be feasible both due to the rarity of NTRK gene fusions, and the current lack of clinical equipoise in this setting. Given the rarity of NTRK fusions, the CGP acknowledges that a basket trial, single-arm design is justifiable.

The evidence for larotrectinib is supported with a pooled analysis of efficacy and safety data from NTRK fusion cancer patients enrolled in the LOXO-TRK-14001, SCOUT and NAVIGATE trials.[1,3,4] The pooled analyses included adult and pediatric patients who were enrolled across the three larotrectinib studies. Included patients were ECOG PS 0-2, with locally advanced or metastatic extracranial solid tumours who had previously received standard therapy when available - 90% of patients in this expanded analysis were ECOG PS 0-1, 54% had received <=1 prior line of therapy, and 32% were less than 15 years old and

51% were older than 40 years. The most common histologies included were STS (n=28, 22.9%), salivary gland (n=19,15.6%), IFS (n=18, 14.8%), Thyroid (n=18, 14.8%) and Lung (N=11, 9.0%)

ORR Efficacy:
In the pooled analysis (n=122), ORR was 81% (95% CI 72%, 88%); 17% of patients achieved a CR and 63% achieved a PR. The median time to response was 1.8 months. At the data cut-off, 84% of responding patients (73% of all patients) remained on treatment or had undergone surgery with curative intent[5,26] As of the 30-July-2018 data cut-off date, the median duration of response had not been reached. The percentage of patients with an ongoing response was 88% at 6 months, and 75% at 12 months from the start of response.[5,26] ORR in patients with CNS tumours was estimated to be 36% (95% CI 13%, 65%); with CR in 14%, PR in 21%, and stable disease in 64% of the patients.[27] ORR was also consistent across all subgroups based on baseline disease characteristics (ECOG status and metastatic cancer status), and number of prior treatment regimens.

The CGP concludes that the ORR of 81%, and the durability of the response observed in a population of patients with advanced solid cancers represents promising and clinically meaningful activity.

Subgroup analysis by tumour type:
ORR by tumour type was available for the extended primary analysis et (n=73) and was consistent across many of the tumour types:

- ORR in patients with STS (23% of total) was 88% and 100% ORR in the subgroup with GIST which was just under 7% of the pooled patients. This response rate is unprecedented in GIST and would be a significant improvement given the unmeet need in this population. Patient advocate group (SCFC) discussed the young age of these patients and the burden involved with lose of limbs from their disease and need for rehab.
- For the subgroup of patients with lung cancer (n=4), the high response rate observed with larotrectinib (75%) is not been previously seen with other available therapies for NSCLC (chemotherapy 30-40%, immunotherapy 10-45%, TKI's 60-70%). The CGP acknowledges that the patient number are limited, however is of the opinion that larotrectinib is anticipated to be clinically superior to chemotherapy in this biomarker-selected subgroup of NSCLC.
- Within the pediatric subgroup (<18 years of age), ORR was 90% (unselected by tumour type). The evidence of efficacy in pediatric and adolescent patients with documented TRK fusions is agreed by the CGP to be clinically remarkable, with median duration of response not being reached in the SCOUT study follow-up. There are currently no commercially available alterative pan-TRK inhibitor for these patients. Of note, larotrectinib is also available in liquid formulation, which is an extremely important consideration for pediatric patients. Access to the liquid formulation allows dosing of infants and young children who could benefit from this therapy.
- There were 6 patients in the extended primary analysis set with Colon cancer among whom a 33% response rate was reported. The CGP agreed that larotrectinib may be of net clinical benefit in pre-treated advanced colorectal cancer harboring a TRK-fusion.
- Other subgroups of patients with other tumour types and small patient numbers (n=1-2) did not respond to larotrectinib (appendix, breast, cholangiocarcinoma, and pancreas). The CGP noted that for the one patient with breast cancer, it was not clear if this was of the secretory subtype which is known to express the NTRK fusion protein. There were suggestions from Registered Clinicians that this targeted therapy would not be an urgent need in breast cancer as many alternative therapies are available and the burden of disease with this mutation rarely becomes metastatic. The CGP further

noted that NTRK-gene fusions are rare in non-colorectal GI cancers. However, standard first-line therapies in this setting, particularly for pancreatic cancer and cholangiocarcinomas, are of limited benefit and associated with significant toxicities.

PFS and OS Efficacy:
After a median duration of follow-up of 19.6 months, the median PFS was 28.3 months (95% CI 9.9, not estimable). In their report, the Submitter acknowledged that this estimate was "not statistically stable due to a low number of progression events, as evidenced by the wide confidence interval".[5] The OS results were only available for the extended primary analysis set (n=73) and performed at the 19-February-2018 data cut-off. In this analysis 86% of patients were alive and 14% had died. After a median follow-up of 14.8 months, the median OS had not been reached. At 12 months, the probability of survival was estimated to be 90%.[5]

Recognizing the limited follow-up and events for the PFS and OS data, and the lack of comparative data, the CGP deems a median PFS of 28.3 months and a median OS which has not yet been reached after 14.8 months of follow-up to be remarkable in a pre-treated population with advanced solid tumours. This efficacy data is consistent with the high ORR and long duration of response observed with larotrectinib in this setting.

Quality of Life
HRQoL was an exploratory objective in the NAVIGATE and SCOUT studies:
- Of the 40 adult patients who completed EQ-5D-5L questionnaire, 73% had and improvement in VAS health score, with 60% reporting a post-baseline score that reached or exceeded the MID of 10 points. Among evaluable patients, 51% had an improvement in VAS health score that lasted for at least two consecutive cycles.[10]
- Of the 40 adult patients who completed EORTC QLQ-C30 questionnaire, 70% had and improvement in global health scores, with 60% reporting improvements that reached or exceeded the MID of 10 points. Among evaluable patients, 41% had an improvement in EORTC QLQ-C30 global health score that lasted for at least two consecutive cycles. EORTC QLQ-C30 global health score improvements were reported for all tumor types.[10]
- Of the 17 pediatric patients who completed PedsQL-Core questionnaire, 88% had improvement in PedsQL total scores, with 76% reporting a best post-baseline score that reached or exceeded the MID of 4.5 points. Among evaluable patients, 65% reported improvements that lasted for at least two consecutive cycles. PedQL total score improvements were observed across tumor types.[10]

Recognizing that the HRQoL data is limited to small numbers of patients, the use of larotrectinib does appear to be associated with an improved HRQoL.

Safety:
Larotrectinib has been found to be safe and tolerable. The majority of the reported adverse events (AEs) were grade 1 or 2, most commonly reported as fatigue, dizziness, nausea and constipation. Treatment-related Grade 3 or 4 AEs occurred in less than 5% of patients. The most common Grade 3/4 AEs included anemia, increase in liver enzyme (ALT and AST) levels, and nausea. Eleven out of the 122 patients (9%) in the Integrated analysis set required dose reductions due to AEs, and all maintained tumour regression on reduced dose. The safety of larotrectinib does not appear to vary by histologic subtype.

Interpretation, Generalizability and Limitations:

The CGP undertook considerable deliberation as NTRK fusions, while rare, are seen in a wide spectrum of adult and pediatric solid tumours. The clinical data supporting the efficacy of larotrectinib, a selective TRK inhibitor, is derived from a pooled analysis of single-arm, basket trials with a histology-agnostic patient population defined primarily by the presence of an NTRK gene fusion.

The CGP considered various limitation associated with the available evidence for the use of larotrectinib in patients with NTRK positive solid tumours and agreed that heterogeneity in the patient selection criteria and trial design (eg. non-comparative, different primary endpoints across 3 pooled trials, small sample sizes, trials are still ongoing) impacts the interpretability of the pooled analysis. Furthermore, there is a lack of evidence to demonstrate the prognostic impact of the NTRK fusion protein, and lack of historical evidence in selected NTRK positive patients to determine historical comparative outcomes with available agents.

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. This is particularly meaningful within the population of patients for which there are no effective systemic treatment options, and/or for whom prognosis is poor [including infantile Fibrosarcoma (IFS), undifferentiated sarcoma, cellular congenital mesoblastic nephroma (CMN), secretory breast cancer (SBC), mammary analog secretory carcinoma of the salivary gland (MASC), high grade gliomas, HCC, pancreatic cancer]. The panel acknowledged some hesitation in determining the comparative effectiveness of larotrectinib within population for who active agents are available or with a relatively more favourable prognosis [CRC (MSS. RAS/BRAF WT), NSCLC, Breast CA: non-secretory, Head and Neck SCC, Melanoma] However, the panel agreed that the ORR efficacy observed in NTRK-fusion selected tumours within these histologies were meaningful.

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 further discussed that caution must be used in interpreting the PFS and OS results. The panel acknowledged the limitation in combining a heterogenous population of patients within one KM curve to determine survival outcomes given the fact that conventionally survival analyses rely on the assumption that a single survival distribution can be used to estimate the survival of all study participants. As such, 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.

Following the posting of the pERC initial recommendation, feedback was received from stakeholders regarding the interpretation of the available clinical evidence within the pERC initial recommendation. Having reviewed the feedback submitted from patient groups, registered clinician groups, the sponsor and PAG, the CGP provided the following additional statements to address questions regarding the clinical effectiveness of larotrectinib.

Related to various feedback addressing the prognostic relevance of the NTRK fusion protein, the CGP further discussed the following.

Based on the opinion of the CGP, the pooled analysis data submitted shows evidence of remarkable and unprecedented efficacy, and safety, across tumour types with NTRK fusion drivers, and across NTRK fusion types in both pediatrics and adults. The CGP interpretation and comments therefore support clinical benefit based upon the histology agnostic efficacy of larotrectinib in tumours harbouring an NTRK gene fusion. The ORR of 81% (95% CI 72%, 88%) and durability of response, observed with larotrectinib is impressive and meaningful, and observed across a wide spectrum of tumour histologies. The CGP further re-iterate that NTRK fusion cancers are rare, and often represent small subgroups within a given histologic cancer type. As such, a basket trial design is considered appropriate and analysis which subdivide the trial data into heterogenous histologic subgroups, are a logistical challenge with respect to economic analyses regarding net clinical benefit. Overall, in the CGP's opinion, the evidence in the pooled analysis is sufficient to demonstrate a tumour agnostic effect and is consistent with the Health Canada indication for larotrectinib.

From a pediatric cancer perspective, we feel strongly that there should be a histology agnostic indication for larotrectinib in children with advanced, recurrent or refractory NTRK driven cancers. The pooled analysis overall response rate of 81% is actually higher in pediatrics with an ORR of 90% in patients across histologic subgroups, with durable responses and minimal toxicity. These unprecedented responses will most certainly translate into PFS benefit for these patients. The current recommendation would exclude some of the children that would benefit most from access to this novel agent, including young children with high-grade CNS tumours. These children have aggressive disease, and limited options. Even radiation therapy is often not feasible in very young children with high grade gliomas and carries risks of devastating neurocognitive outcomes. Separate response data for primary CNS NTRK driven tumours has been submitted, with documented radiologic responses by RANO criteria in these rare patients who are in desperate need of novel, and tolerable therapies. In young children with relapsed or refractory high-grade glioma, the chance of long-term survival is well below 20%. Among initial patients with NTRK fusion positive primary CNS tumours, 14% have achieved complete response, with 36% achieving response by RANO. These patients should not be excluded from access to this therapy.

Similarly, children with multiple relapsed or refractory NTRK driven thyroid carcinomas desperately need access to larotrectinib to avoid additional invasive surgical resection attempts and repeated radio-active iodine therapy that carries risks of late effects and secondary malignancies. Although these patients are rare, their potential to achieve durable response with excellent quality of life with net clinical benefit if they access to larotrectinib is almost certain with reported ORR benefit of 100% in thyroid carcinoma in the pooled analysis.

Related to feedback addressing the burden of illness in patients with an NTRK fusion protein positive solid tumour and the availability of treatment options among different settings, the CGP further discussed the following.

The CGP agrees with the feedback that the activity of larotrectinib would be expected to behave as other current histology-specific targeted agents (such as ALK or EGFR). This is based both upon the evidence available - the very high response rates observed with larotrectinib in the presence of an NTRK gene-fusion – and clinical opinion, recognizing

that these ORR surpass expected response rates with alternate systemic therapies in advanced disease.

1.3 Conclusions

From a histology-agnostic, biomarker-driven perspective, larotrectinib offers a clinical benefit in good performance status adult and pediatric patients with advanced solid tumours that harbour an NTRK-gene fusion. The CGP has acknowledged the various limitations associated with the available evidence and agree that the observed ORR are unprecedented across the wide spectrum of included tumour histologies.

In the absence of comparative evidence to understand the incremental magnitude of benefit associated with larotrectinib across the variety of tumour settings, the CGP agreed that there is likely more certainty of benefit among populations for whom the burden of illness and/or need for effective therapeutic agents is high. The CGP further acknowledged that this approach is supported by input from Registered Clinicians. Based on this, the CGP made the following two site specific conclusions on the net clinical benefit of larotrectinib.

The intent of the two site-specific conclusions made by the CGP was not to contradict the CGP's opinion supporting a tumour agnostic effect. It was a consequence of the limitations raised by the Methods team with respect to absence of comparative evidence to analyze the incremental magnitude of benefit with larotrectinib among tumours where treatments were available; hence, the CGP offered site-specific conclusions based on unmet need and lack of alternative options for selected tumour types, prioritizing tumour types listed in Table A. The CGP further note that the reasons supporting the pERC initial recommendation limiting larotrectinib for NTRK gene fusions observed only in salivary gland tumours, soft tissue sarcomas and pediatric patients with congential mesoblastic nephroma or infantile fibrosarcoma remain unclear to the CGP.

The CGP conclusions also reiterated that it would be reasonable to provide reimbursement for larotrectinib for the treatment to all patients with NTRK fusion cancers who have either failed upfront therapy, have locally advanced disease not amenable to resection or have no alternative therapy with an acceptable toxicity profile.

Site-specific Conclusions:
The CGP concluded that there is a net clinical benefit to larotrectinib in the treatment of the following patient populations (see table A below) based on the results of a pooled analysis which demonstrated a large and clinically significant benefit in ORR, a safe and tolerable toxicity profile and meaningful improvements in QoL in most patients. Given the poor prognosis of these patient populations and the lack of effective treatment options, the CGP agreed that patients will derive a meaningful net clinical benefit from treatment.

Furthermore, the CGP concluded that there is a net clinical benefit with the use of larotrectinib for pediatric patients with NTRK fusions, across all cancer types, who have metastatic or locally advanced disease which is not amenable to surgical resection, or in whom no satisfactory alterative therapy is available. This is based on unprecedented response rates documented in the pediatric phase I/II trial of larotrectinib monotherapy, with minimal toxicity. It is also clear from parent / patient advocacy group and registered clinician input that the use of larotrectinib in the treatment of NTRK fusion pediatric cancers is fully supported and offers a true breakthrough in care.

Within the pediatric population, the CGP recommendation was for all NTRK driven advanced (relapsed/refractory or no alternative therapy) pediatric cancers specifically because there is a

lack of available alternative options for these patients. Pediatric cancers overall have low mutation burden, and typically do not respond to immunotherapy agents. Similarly, there are few other targeted therapies with proven efficacy in pediatric cancer overall, but specifically NTRK fusion cancers typically lack other actionable molecular targets in pediatrics. Alternative conventional chemotherapy regimens are limited, and ineffective, in these patient groups. Access to larotrectinib may help avoid recurrent, invasive radical neck dissections and repeated exposure to radioactive iodine for young children with thyroid cancer, as it may also help avoid limb amputations in children with IFS or sarcoma. It may provide a treatment option to children with high grade gliomas who are unable to received high-dose cranial radiation due to their young age.

Overall, there are no alternative commercially available NTRK inhibitors in Canada. Larotrectinib provides a safe, tolerable and effective therapy for young patients without other therapy options. The possibility to benefit from larotrectinib is accessible even to very young patients due to its availability in a liquid formulation.

Table A:

Rational	Included tumour types	Recommended systemic treatment approach in advanced disease
Pediatric patients with NTRK+ advanced solid cancers	Infantile Fibrosarcoma (IFS) Cellular congenital mesoblastic nephroma (CMN) Secretory breast cancer (SBC) Mammary analog secretory carcinoma of the salivary gland (MASC) Papillary thyroid carcinomas High grade gliomas Undifferentiated sarcoma Any other NTRK+ advanced solid tumours not otherwise specified	Larotrectinib therapy should be considered as part of first-line therapy
Adult patients with an NTRK+ advanced solid cancers who have an unfavourable prognosis and limited therapy options	Papillary thyroid Soft Tissue Sarcoma Cholangiocarcinoma Primary Unknown	Larotrectinib therapy should be considered as part of first-line therapy
	High grade gliomas HCC Pancreatic cancer	Larotrectinib therapy should be considered as part of first-line therapy
	GIST – wild type (adult and pediatric)	Larotrectinib therapy should be considered as part of first-line therapy

The CGP concluded that there may be a net clinical benefit to larotrectinib in the treatment of the following patient populations (see Table B) based on the results of a pooled analysis which demonstrated a large and clinically significant benefit in ORR, a safe and tolerable toxicity profile and meaningful improvements in QoL in most patients. The Panel was however unable to determine the magnitude of this clinical benefit given the availability of alternative treatment options for whom comparative evidence was unavailable.

Among the population of patients with cancers which have an alternative treatment option, the CGP re-iterated that there may be a net clinical benefit. As an example, despite the availability of active agents, there is no known agent with an 80% response rate in lung cancer. The CGP agree that patients should be permitted to access this highly active therapy given the lack of curable or highly effective options, including chemotherapy, immunotherapy, chemo-immuno combinations. In addition, all other targeted therapies in lung cancer targeting EGFR, ALK and ROS1 have lower response rates and have demonstrated major activity and are superior to

chemotherapy. Despite small numbers, a greater signal is seen in advanced lung cancer patients with TRK fusions.

Table B:

Rational	Included tumour types	Recommended systemic treatment approach in advanced disease
Adult patients with an NTRK+ advanced solid cancers, have relatively better prognosis and/or better alternative systemic therapy options	Adult GIST MSI-H CRC	Larotrectinib therapy should be reserved as a second-line therapy and beyond until evidence supporting superiority over current first-line therapy is available
	CRC (MSS. RAS/BRAF WT) NSCLC Breast CA: non-secretory Head and Neck SCC Melanoma	Larotrectinib therapy should be reserved as a second-line therapy and beyond until evidence supporting superiority over current first-line therapy is available.

In making these conclusions the CGP also considered:

- the need for implementation of validated testing for NTRK gene fusions in at-risk patient groups.
- The panel further recommends that careful consideration is given to reimbursement criteria so that patients who could potentially benefit from larotrectinib are not excluded. Specifically, the panel concludes that it would reasonable to provide reimbursement for larotrectinib for the treatment of all patients with NTRK fusion cancers who have either failed upfront therapy, have locally advanced disease not amenable to resection **or** have no alternative therapy with an acceptable toxicity profile, which may occur in the upfront setting.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by members of the pCODR Lung, Breast, Gastrointestinal, Pediatric, Sarcoma and Endocrine Clinical Guidance Panels (CGP). It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

The NTRK genes encode the neurotrophin family of receptors. NTRK gene fusions are identified as the oncogenic driver in up to 1% of all solid cancers. Larotrectinib is an oral selective inhibitor of inhibitor of tropomyosin kinase receptors TrkA, TrkB, and TrkC, which are encoded by NTRK 1, 2 and 3.

NTRK oncogenic fusions arise from exact intrachromosomal or interchromosomal rearrangements that juxtapose the kinase domain-containing 30 region of NTRK with the 50 region of NTRK gene partners.[28] Preclinical data demonstrated that chimeric oncogenic fusions may lead to partial or complete deletion of the immunoglobulin-like domain of TRK, which has an inhibitory influence on downstream signaling pathways in the absence of activating ligands.[29] While available literature demonstrates that the NTRK gene fusions are oncogenic drivers in various cancers, there is limited data to directly indicate how the presence of the genetic aberration may affects a patient's prognosis (see Section 7.1).

Although reported to be responsible for up to 1% of all solid cancers,[30] NTRK oncogenic fusions are observed in variable frequencies across a spectrum of pediatric and adult cancers, with some uncertainty regarding exact frequencies.[31] Different studies have reported varying frequencies which may be explained by the number of patients screened and NTRK fusion detection techniques. A variety of techniques are used to detect the NTRK fusions protein and are described further in section 8.1 of this report.

Table 1. Prevalence of NTRK gene fusion in solid tumours

Tumor type	Prevalence (%)	Detection methods	References
Appendiceal cancer	2/97 (2%)	MSK-IMPACT/sequenum	Braghiroli et al. (65)
Cholangiocarcinoma	1/28 (4%)	DNA seq	Ross et al. (66)
CRC	13/346 (4%)	NGS	Pietrantonio et al. (22)
CRC MSI-H	10/13 (76.9%)	NGS	Pietrantonio et al. (22)
Melanoma	1/374 (0.3%)	RNA-seq	Stransky et al. (12)
GBM	3/115 (3%)	AMP	Zheng et al. (27)
HNC	2/411 (0.5%)	RNA-seq	Stransky et al. (12)
Infantile fibrosarcoma	2/4 (50%)	FISH	Knezevich et al. (63)
Low-grade glioma	2/461 (0.4%)	RNA-seq	Stransky et al. (12)
Lung adenocarcinoma	3/91 (3.3%)	NGS/FISH	Vaishnavi et al. (14)
MASC	2/3 (66 %)	FISH/RT-PCR	Skalova et al. (35)
PTC	4/33 (12%)	RT-PCR	Brzezianska et al. (67)
PHGG	28/127 (22%)	NGS	Wu et al. (54)
Polycystic astrocytoma	3/96 (3%)	WGS	Jones et al. (55)
SBC	12/13 (92%)	RT-PCR	Tognon et al. (34)
Spitzoid melanoma	23/140 (16%)	NGS	Wiesner et al. (56)

Abbreviations: AMP, anchored multiplex polymerase chain reaction; CRC; colorectal cancer; DNA seq, DNA sequencing; GBM, glioblastoma multiforme; HNC, head and neck cancer; MASC, mammary analog secretory carcinoma; MSI-H, microsatelite instability-high; NGS, next-generation sequencing; PHGG, pediatric high-grade glioma; PTC, papillary thyroid carcinoma; RNA-seq, RNA sequencing; RT-PCR, reverse transcriptase polymerase chain reaction; SBC, secretory breast carcinoma; WGS, whole-genome sequencing.

"Reprinted from Clinical Cancer Research, 2018, 24/23, 5807-5814, Ed S. Kheder, David S. Hong, Emerging Targeted Therapy for Tumors with NTRK Fusion Proteins, with permission from AACR".

Lung, colorectal and breast cancer represent the three most common cancer diagnoses in Canada (see Table 2).

- In NSCLC, NTRK fusions (approximately 0.1% to 1%)[23,25,32] are less common than other oncogenic gene rearrangements that involve the anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1(ROS1), and RET proto-oncogene (RET), which occur at frequencies of approximately 4% to 6%, 1% to 2%, and 1% to 2%, respectively.[33-35]
- The NTRK mutation is also quite rare in breast cancer with the exception of the rare subtype of secretory breast cancer where the prevalence of NTRK fusion has been reported to be 92%.
- NTRK-gene fusions are also rare in sporadic colorectal cancers (2-3%),[23] appearing to be more common in colorectal tumours with high levels of microsatellite instability (MSI-H), and mutually exclusive of RAS and BRAF mutations (which represent about 55% of mCRC). [36]
- The NTRK mutation is uncommon in adult sarcomas (1%); it is found in higher frequency in GIST[2], particularly wild-type GIST (lacking mutations in KIT and PDGFRA)
- NTRK-gene fusions are observed in 12% of adults with primary thyroid cancers.[24]

While the frequency of NTRK fusions is low in common cancer types, NTRK3 fusions are nearly ubiquitous among rare cancer types such as mammary analog secretory carcinoma and infantile fibrosarcoma (IFS).[23,37] In pediatric oncology, NTRK fusions are pathognomonic of specific, rare cancers including IFS (91-100%))[38] and cellular congenital mesoblastic nephroma (83%).[23] NTRK fusions are also commonly observed in several other very rare pediatric cancers, including secretory breast cancer (92%)[39] and mammary analog secretory carcinoma of the salivary gland (100%).[40] In addition, there are significant numbers of NTRK fusion cancers among children with papillary thyroid carcinoma (9.4-25.9%),[24,41] undifferentiated sarcomas (1%, frequency in adult vs pediatric not specified),[42] high grade gliomas (7.1%),[23] inflammatory myofibroblastic tumours and rarely in acute leukemia.

Table 2. Incidence and mortality associated with solid tumours among Canadians (2018)[43]

	Projected incidence		Projected mortality		5-year net survival
	Cases	ASIR*	Deaths	ASMR*	%
Lung and bronchus	28,600	69.9	21,100	51.4	17
Colorectal	26,800	66.3	9,400	23.1	64
Breast	26,500	68.1	5,000	12.6	87
Prostate	21,300	110.4	4,100	23.8	95
Bladder	8,900	21.8	2,400	5.7	73
Uterus (body, NOS)	7,300	35.7	1,150	5.3	84
Melanoma	7,200	18.5	1,250	3.1	88
Thyroid	7,100	19	220	0.5	98
Kidney and renal pelvis	6,600	16.5	1,900	4.6	67
Pancreas	5,500	13.5	4,800	11.9	8
Oral	4,700	11.9	1,250	3.1	63
Stomach	3,500	8.6	2,100	5.1	25
Brain/CNS	3,000	7.8	2,400	6	24
Ovary	2,800	13.7	1,800	8.2	44
Liver	2,500	6.1	1,200	3	19
Esophagus	2,300	5.7	2,200	5.3	14
Cervix	1,550	8.3	400	2	73
Larynx	1,150	2.8	440	1.1	63

	Projected incidence		Projected mortality		5-year net survival
Testis	1,100	6.1	45	0.2	96
All other cancers	19,500	48.5	10,400	25.5	—

ASIR=age-standardized incidence rate, ASMR=age-standardized mortality rate, CNS=central nervous system, NOS=not otherwise specified
* Rates are age-standardized to the 2011 Canadian population and are per 100,000 males and females

Childhood cancer accounts for less than 1% of all new cancer cases in Canada. Between 2009 and 2013, there were 4,715 new cases of cancer in children 0–14 years of age in Canada (average of 943 cases per year). Between 2008 and 2012, there were 595 cancer deaths in children 0–14 years of age in Canada (average of 119 deaths per year). Brain and central nervous system cancers account for 19% of cancers and 34% of deaths, neuroblastoma and other peripheral nervous cell tumours account for 11% of deaths.[44]

The most common types of solid tumours found in adolescents (15-29 years) include thyroid (16%), testicular (13%) and melanoma (8%), while the majority of cancer deaths (from solid tumours) in adolescents are attributed to brain and central nervous system cancers (15%) and bone cancers (11%).[44]

2.2 Accepted Clinical Practice

Historical evidence is not available to determine the prognostic impact of the NTRK fusion protein. Retrospective evidence is being collected in the Voyager-1 study (see Section 6.4) to assess the historical response of patients with the NTRK fusion protein who are treated with available standard options.[5] Results are however not currently available.

There is currently no reimbursed agent that targets the NTRK pathway. Among adult cancers, defining accepted clinical practice is difficult as NTRK gene fusions can be observed in a multitude of solid cancers. Patients with locally advanced or metastatic solid tumours are currently largely treated with standard of care (chemotherapy, immunotherapy and/or targeted therapy) as defined by their primary disease site (see Table 3). Ultimately, many of these cancers have a poor prognosis, and patients who progress on upfront therapies will have limited subsequent therapeutic options. Table 3 has categorized the spectrum of solid cancers with NTRK gene fusions by the frequency of NTRK gene fusions, by prognosis as determined by number of alternative standard therapies available.

For patients with pediatric NTRK fusion cancers which are refractory to upfront therapy there is no standard of care at relapse. In addition, for infants with locally advanced, unresectable IFS, standard upfront conventional cytotoxic chemotherapy is poorly tolerated, has limited efficacy and is associated with significant morbidity. Access to larotrectinib for this small group of young patients may facilitate gross total resection with minimal morbidity, potentially avoiding the need for limb amputation.

Table 3. NTRK gene fusion frequency and prognosis as determined by number of alternative standard therapies available

Epidemiology/ NTRK gene fusions	Examples	Prognosis	Currently recommended treatments
Frequent cancer histologies with rare NTRK gene fusions (<5%)	NSCLC	Favourable	Anti-PD-1 therapy (immunotherapy) Chemotherapy Anti-PD-1/Chemotherapy combinations Biomarker-based targeted therapies
	Colorectal cancer		Biomarker-based targeted therapies
	Head and neck		Chemotherapy Biomarker-based targeted therapies
	Melanoma		Immunotherapy, biomarker-based targeted therapies
	Breast (non-secretory)		Chemotherapy, biomarker-based targeted therapies
	High grade gliomas	Poor	Limited/No effective therapies - *may include chemotherapy for gliomas and pancreatic cancer, and small molecule inhibitors for HCC*
	HCC		
	Pancreatic cancer		
Less common cancers with relatively common NTRK gene fusions (5%–25%)	Papillary thyroid carcinoma	Poor	Radioiodine abalation therapy, chemotherapy Targeted therapies
	Soft tissue sarcoma (STS)		
	Biliary cancer		
	Cholangiocarcinoma	Poor	Limited/No effective therapies - *May include chemotherapy*
	Primary unknown		
	MSI-H CRC	Favourable	Chemotherapy, biomarker-driven targeted therapy, immunotherapy (not funded in Canada) Biomarker-based targeted therapies for GIST (for CKITm)
	GIST		
Rare cancers with relatively common NTRK gene fusions (>75%)	Secretory breast carcinoma – pediatric and adult	Variable	Limited/No effective therapies *- (surgery if possible and with acceptable morbidity) in CMN and IFS*
	Cellular congenital mesoblastic nephroma (CMN) - pediatric		
	Mammary analog secretory carcinoma of the salivary gland (MASC) – adult and pediatric		
	Infantile fibrosarcoma (IFS) – pediatric		

2.3 Evidence-Based Considerations for a Funding Population

Larotrectinib is a highly selective, potent, ATP-competitive, and small-molecule pan-TRK inhibitor with an IC50 in the low nanomolar range whose safety and efficacy was evaluated in three separate phase I-II clinical trials and which is being evaluated for reimbursement in the current CADTH-pCODR review. Other NTRK targeting therapies like entrectinib, a highly potent oral ATP-competitive, pan-TRK, ROS1, and ALK inhibitor are also under investigation in other trials.[28]

The requested reimbursement population for larotrectinib is for the treatment of adult and pediatric patients with locally advanced (unresectable or where surgical resection is likely to

result in severe morbidity) or metastatic solid tumours harbouring a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion. Additional reimbursement criteria requested by the submitter include: age ≥ 1 month, ECOG score of ≤3 (or equivalent Lanksy score for pediatrics), tumour harbouring NTRK1, NTRK2 or NTRK3 gene fusion confirmed by a validated diagnostic testing method and patients eligible for larotrectinib should have no satisfactory alternative treatments or have progressed following treatment.

2.4 Other Patient Populations in Whom the Drug May Be Used

From a histology-agnostic, biomarker-driven perspective, larotrectinib appears to provide a clinical benefit in good performance status adult and pediatric patients with advanced solid tumours that harbour an NTRK-gene fusion. Based on this, other patients with a solid tumour that harbours the NTRK fusion protein and who were not included in the trials evaluating the efficacy and safety of larotrectinib are likely to derive benefit with larotrectinib treatment. A randomized, controlled phase 3 trial in this setting would not be feasible both due to the rarity of NTRK gene fusions, and the current lack of clinical equipoise in this setting.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The patient input for 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 was provided through a collaboration of seven patient groups. The participating groups included:

- Canadian Cancer Survivor Network ("CCSN")
- Colorectal Cancer Canada ("CCC")
- Lung Cancer Canada ("LCC")
- Neuroblastoma Canada ("NC")
- Ontario Parents Advocating for Children with Cancer ("OPACC")
- Sarcoma Cancer Foundation Canada ("SCFC")
- Thyroid Cancer Canada ("TCC")

Draft survey questions were sent to representatives from each group, who provided detailed feedback for the creation of the patient input survey. Each group was also asked to distribute the completed survey to their networks. CCC reached out to the clinical trial principal investigator at MD Anderson on January 17, 2019 to help identify patients who would be willing to provide their experience with the therapy under review by participating in a telephone interview, as well as complete the CCSN online patient survey. CCC also reached out to an online larotrectinib support group in the United States (U.S.) requesting patients to contact the patient groups if interested in providing their experience with larotrectinib. LCC conducted an environmental scan of online forums and also conducted an interview. The opinions on previous and current treatments of patients with lung cancer were also included in this submission. Because this particular genetic mutation is so rare, and the treatment is not available in Canada, LCC indicated that they had a difficult time finding patients and caregivers with this experience. SCFC collected data from Canadian patient respondents who received their treatment in the U.S.

The patient input was obtained through a survey conducted from December 2018 to February 2019 on SurveyMonkey, which was publicized on CCSN's website (survivornet.ca), social media (Facebook & Twitter) and sent to the CCSN mailing list. In addition to the survey, CCC, LCC, NC and SCFC also conducted qualitative interviews with patients who have experience with larotrectinib.

The patient groups collectively reported on 14 patient and two caregiver respondents with experience with larotrectinib.

The survey was completed by six (6) anonymous individual respondents, which included five (5) patient respondents and one (1) caregiver respondent. All patient respondents reported experience with larotrectinib. The six (6) respondents are listed below, along with the terminology used to refer to them in this section on where applicable.

- two (2) thyroid cancer patients ("Patient 1" and "Patient 3")
- one (1) lung cancer patient & one (1) lung cancer caregiver ("Patient 6" and "Caregiver 1")
- one (1) patient with salivary duct carcinoma ("Patient 2")
- one (1) patient with secretory carcinoma of the parotid gland ("Patient 5")

Four of the patient respondents (Patients 1, 2, 3 and 5) received larotrectinib as part of a clinical trial at MD Anderson in Houston, Texas. The lung cancer caregiver, despite filling out the survey in full, did not provide any indication that their patient was tested or treated specifically for NTRK gene fusion or if they have experience with larotrectinib. As such those responses have been omitted from this submission.

As it relates to the qualitative interviews, CCC spoke directly with six (6) patients who provided thoughtful, compelling and high-quality telephone interviews (five of whom also completed the online survey):

- two (2) thyroid cancer patients (Patient 1 & 3)
- two (2) salivary gland cancer patients (Patient 2 & 4)
- one (1) secretory cancer of the parotid gland patient (Patient 5)
- one (1) non-small cell lung cancer patient (Patient 6)

LCC collected input from four (4) patient respondents through an environmental scan and conducted an interview with one (1) patient respondent. Of this group, there were three male and two female patients. One male patient provided input via a phone interview and data from the remaining four was collected via environmental scanning. One patient is located in Brazil and the remaining four are in the Unites States.

Source	Gender	Age	Patient / Caregiver
Environ Scan	M	62	Patient
Environ Scan	M	N/A	Patient
Environ Scan	F	N/A	Patient
Environ Scan	F	N/A	Patient
Interview	M	61	Patient

NC conducted a qualitative interview with the parents of a child taking larotrectinib. SCFC interviewed two (2) patient respondents with direct experience with larotrectinib, as well as two (2) caregivers. SCFC responses also include general sarcoma cancer information, which were arrived at by sharing personal experience, as well as the collective experience of SCFC's membership and community.

From a patient's perspective, the presence of a specific genetic tumour biomarker (rather than the site at which the cancer originates) is of paramount importance and unites the various disease sites containing the genetic mutation. Patient respondents have noted that personalized medicines have changed the outlook for cancer patients who have actionable driver mutations. The patient groups in this submission noted that diagnostic testing for the NTRK gene fusion is currently not available or funded in Canada. With the increasing importance of genomic profile testing and personalized medicine, this form of testing is needed. All patient respondents in this submission had genomic testing showing they had the NTRK gene. The patient respondents all have accessed previous therapies for the treatment of their respective cancers and had varying symptoms affecting their daily life.

Patient respondents would expect improved outcomes of larotrectinib to include: improved symptoms, including reduction in pain, increase in mobility, and ease of breath; better survival rates; better quality of life while effectively controlling their disease and easier form of treatment modality. Patient respondents reported the following treatment-induced side effects with larotrectinib: elevated ALT/AST levels, tinnitus, swollen ankles, withdrawal-like symptoms, overstimulation, fatigue, sensitivity to light, and flu-like symptoms – all of which were considered by respondents to be tolerable and relatively minor. According to the patient respondents, this treatment has delivered a clinically meaningful response in their cancer. Their disease has either resolved completely, significantly or to a great extent, while managing to maintain a high level of quality of life. For those patients who were experiencing cancer-induced symptoms prior to starting Larotrectinib, respondents reported a significant improvement in those symptoms after

starting the therapy. Additionally, patient respondents appreciate an easily administered oral therapy in the comfort of their homes.

Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from the patient advocacy groups.

Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Neurotrophic Tyrosine Receptor Kinase (NTRK) Locally Advanced or Metastatic Solid Tumours

When asked what symptoms or problems that respondents experienced with their cancer that affected their day-to- day living and quality of life, the patient respondents in the survey reported the following:

- Thyroid Patient 1 experienced no symptoms.
- Thyroid Patient 3 experienced fatigue.
- Lung Patient 6 experienced difficulty breathing.
- Salivary Duct Patient 2 experienced fatigue and pain.
- Parotid Gland Patient 5 experienced fatigue, pain and swelling.

According to CCSN, fatigue seemed to be the most common symptom affecting daily life amongst the respondents. Three patient respondents cited fatigue as the most negative effect in their daily lives, and two patient respondents also reported pain affecting their day-to-day living. One patient respondent reported that they are currently symptom-free. Based on the above reporting, these symptoms affected the respondents' quality-of-life and their ability to enjoy life.

CCC asked the interviewed patient respondents if they had any cancer-induced symptoms before starting larotrectinib. With the exception of the thyroid patient respondent, who had none, five patient respondents reported the following symptoms: pain, fatigue, incontinence, shortness of breath, headaches/dizziness and swelling (pain being the most commonly reported symptom), which was consistent with the survey responses.

LCC indicated that a diagnosis of lung cancer affects not only the patients but their loved ones too. With the low survival rate of 17% many caregivers worry whether the diagnosis is a death sentence and how they would cope. Caregivers may also experience stigma because of the negative implications associated with lung cancer. With some unconscious attitudes directed towards the patients and sometimes their loved ones, caregivers feel emotionally burdened and may even isolate themselves. This could lead to anxiety, worry and even depression.

SCFC noted that sarcoma is an invasive and aggressive cancer. There are many subtypes (over 50 soft tissue sarcomas alone); as such, there are many different patient experiences. Sarcoma affects Canadians of all ages but primarily children and young adults, so we often hear of young people showing athletic promise or who have physical jobs being unable to continue work or leisure activities due to their disease. Patients are either candidates for surgery, which can be in various forms but may include losing a limb if the sarcoma is in the arm or leg, or they may be candidates for chemo and other targeted treatments. In the event that a patient is a candidate for surgery, a long journey

begins where there is often significant rehab and becoming comfortable with prosthetics. In the event that surgery is not an option and a patient embarks on chemo or treatment of some kind, they are often unable to participate in work or day to day activities due to treatment schedule, recovery time, side effects, etc. Sarcoma patients experience fatigue, severe cough, severe pain, insomnia, loss of appetite, vomiting, diarrhea, shortness of breath and difficulty breathing, among other symptoms. SCFC has heard from many patients who have had to go into significant debt to access treatments, resulting in the loss of their home, the breakup of their marriage, the end of a career they had spent many years training for, the onset of depression and other mental illness, and generally a significantly reduced quality of life.

3.1.2 Patients' Experiences with Current Therapy for Neurotrophic Tyrosine Receptor Kinase (NTRK) Locally Advanced or Metastatic Solid Tumours

CCSN asked respondents about treatments they have received previously or currently to treat their disease:

- Thyroid Patient 1 received surgery, radiation, a suppression dose of synthroid, and now larotrectinib as part of a clinical trial.
- Thyroid Patient 3 received surgery, chemotherapy, radioactive iodine treatment, and now larotrectinib as part of a clinical trial.
- Lung Patient 6 received "targeted therapy" though did not define which.
- Salivary Duct Patient 2 received surgery, radiation therapy, and larotrectinib.
- Parotid Gland Patient 5 received surgery, targeted therapy, and larotrectinib.

In follow-up to the above, CCC confirmed that all interviewed patient respondents accessed previous therapies for the treatment of their respective cancers. Thyroid Patient 1 had accessed a Phase I study whose side effects had induced significant toxicities that included nausea, diarrhea, skin irritation and their body hair turning white. Salivary Duct Patient 2 had accessed multiple surgeries in addition to radiation. Thyroid Patient 3 had accessed radiation, radioactive iodine and gamma knife radiosurgery for brain metastases. Patient 4 had accessed surgery and radiation. Parotid Gland Patient 5 had a partial resection of their primary tumour but refused any additional treatments, except for larotrectinib. Lung Patient 6 had accessed a checkpoint inhibitor, chemotherapy, and radiation for the treatment of his non-small cell lung cancer (NSCLC). All patient respondents reported having exhausted therapeutic options for the management of their disease. They were, therefore, required to explore a clinical study.

LCC indicated the current first line standard of care for lung cancer patients with a NTRK gene fusion is chemotherapy or immunotherapy for those that are PDL-1 positive. Patients with the NTRK fusion are unlikely to have other actionable mutations. The use of chemotherapy has been well documented in other submissions and only a summary is provided here. Chemotherapy works to shrink and inhibit further growth of the tumor. Patients treated with chemotherapy experienced side effects that interfered with daily activities. While some patient's experienced minimal symptoms, many reported side effects such as nausea, vomiting and extreme fatigue. Patients also had to deal with the inconvenience of multiple hospital visits for the intravenous infusion as well as the toxicities and after effects associated with the treatment. One patient respondent summarizes it as, "*I spend half my time between infusions recovering from the side effects, a short time being able to function and then the rest of the time dreading the start of the cycle*." LCC noted that, in general, immunotherapy has less side effects than chemotherapy and allows patients to have a high quality for life. Patient respondents reported zero to mild side effects that were easily managed. Some had stronger side effects that had to be managed either by OTC or prescription drugs. Many found that the

treatment was tolerable and did not interfere with day to day life. Immunotherapy also allowed patients to get out of bed and find a "new normal". In some cases, patients developed immune related side effects such as pneumonitis and had to be placed on prednisolone, in more severe cases the treatment resulted in abnormal thyroid hormone levels and patients were subsequently put on thyroid supplements. LCC posited that targeted therapies have changed the paradigm for lung cancer treatment. To illustrate this point, LCC found that targeted therapies are what have allowed one patient respondent to become a 10-year lung cancer survivor and advocate. Through her advocacy, she has helped support lung cancer patients and their families. Another patient respondent, a five-year lung cancer survivor didn't think she would still be here to see her kids grow up, but because of targeted therapy she is about to see here eldest enter university. Targeted therapy also allowed a third patient respondent to continue his work, treating patients with multiple sclerosis. It enabled him to get back to as normal a life as possible with his wife and kids. In his words the respondent said: "*Targeted treatment has allowed me to stay involved in all aspects of my life… I can be the father, be the doctor, be the researcher I've always been*."

SCFC found that while some sarcoma patients may be candidates for surgery, which can alleviate or arrest their disease effectively, most soft tissue sarcoma patients are struggling to find effective treatments. Many of the chemotherapies and targeted treatments currently available cause significant side effects which can have a severely adverse effect on a patient's quality of life and ability to participate in family and societal activities.

3.1.3 Impact of Neurotrophic Tyrosine Receptor Kinase (NTRK) Locally Advanced or Metastatic Solid Tumours and Current Therapy on Caregivers

LCC reported that with the physical burden this disease and treatments take on patients, caregivers are involved in various activities to help patients cope with the symptoms, treatment, side effects and even coordination of care. Apart from the physical aspects, caregivers also experience an emotional toll, which can affect not just the care they provide their loved ones leading to a lower quality of life not just for the caregiver but the patient as well if not addressed properly. Loved ones worry about the extent of disease at the time of diagnosis and about the ultimate outcome or possibility of survival. SCFC further noted that caregivers are sometimes placed in a position of having to care for a very ill child/partner/parent and that process often takes them away from work and other activities.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Larotrectinib

A. Patient Expectations with Larotrectinib

CCC indicated that all six patient respondents expressed a common sentiment throughout their interviews, which include: their desire to access a therapy that would promote quality of life while effectively controlling their disease. The respondents felt they should be permitted to resume their daily activities, be productive members of society by being gainfully employed, spend quality time with their children/families, be socially engaged and have the ability to take vacations/outings without the threat of treatment-induced toxicities compromising quality of life. LCC supported these expectations and added that improved outcomes would also include better survival rates, improved symptoms and easier form of treatment modality. SCFC stated sarcoma cancer patients often experience quick disease progression that, without intervention, will halt their lifestyle and activity

and eventually result in death. Given the lack of long-term effective treatments available to soft tissue sarcoma patients, many patients would describe a reduction in pain, increase in mobility, and ease of breath as a significant improvement.

B. Patient Experiences with Larotrectinib

CCSN reported that the five patient respondents in the survey all reported having experience with larotrectinib. The five patient respondents taking larotrectinib all indicated a significant improvement in their symptoms and their overall outcomes as a result of taking larotrectinib. Moreover, all five patient respondents cited that they are better able to control their symptoms on larotectinib than previous forms of therapy. All five patient respondents also reported the drug's ease of use being a benefit. Three patient respondents (Thyroid Patient 1, Lung Patient 6 and Salivary Gland Patient 2) reported a significant reduction in side effects compared to previous medications or treatments.

Four out of five patient respondents have noticed a slowing of their disease progression, with some noting:

- Thyroid Patient 1: "*[…] 34% reduction of my tumour sizes at my 2 month scan. Every known tumour except for one has decreased in size*."
- Parotid Gland Patient 5: "*Started loxo in June 2018 and the tumour is reduced by 70 percent*."
- Salivary Duct Patient 2: "*Saved my life. I have 85 percent resolve*."

In regards to adverse effects, four patient respondents reported varying symptoms while one patient reported no adverse symptoms while taking larotrectinib. The following were direct quotes:

- Salivary Duct Patient 2: "*Withdrawal symptoms are a pain*."
- Parotid Gland Patient 5: "*Significant flu-like symptoms […] especially in the evening before it's time for the PM dose. Another is weight gain*."
- Thyroid Patient 1: *"[…]45 minutes after my morning dose is a rush of over stimulation. Almost like I've had too much coffee and become very jittery. It begins to fade at 2-3 hours and drops at the 4 hour mark*."

To further illustrate the patient experience with larotrectinib, CCC provided a summary table for six patients undergoing the therapy under review at MD Anderson or Avera Treatment Centre. The patient respondents accessed the therapy through a clinical trial.

LAROTRECTINIB PATIENT INTERVIEWS						
Interview Date & Time	**PATIENT 1** March 4, 2019 9:30 – 10:30 a.m. ET	**PATIENT 2** March 4, 2019 11:00 a.m. – 12:00 p.m. ET	**PATIENT 3** March 4, 2019 12:30 – 1:30 p.m. ET	**PATIENT 4** March 5, 2019 2:00 – 3:00 p.m. ET	**PATIENT 5** March 11, 2019 11:00– 12:00 p.m. ET	**PATIENT 6** March 19, 2019 11:00-12:00 p.m. ET
Gender & Age	**Male, 37 years**	**Male, 61 years**	**Female, 48 years**	**Male, 37 years**	**Female, 70 years**	**Male, 45 years**
City & State	Houston, Texas	Oklahoma City, Oklahoma	Opelousas , Louisiana	Monticello, Georgia	Plymouth, Indiana	Tea City, Outside of Sioux Falls, South Dakota,
Marital Status	Married, 3 children	Married, No Children	Married, No Children	Married, 5 children	Single, No Children	Married, 2 Children
Treatmen t Centre	MD Anderson	MD Anderson	MD Anderson	MD Anderson/Inova	MD Anderson	Avera Treatment Centre
A. Type of Cancer **B. Date of first Dx?** **C. And date of metastatic diagnosis**	A. Papillary Thyroid Carcinoma B. First diagnosed March 2009 C. Metastatic Diagnosis August 2014	A. Salivary Gland Cancer B. October 2014 C. March 2016	A. Papillary Thyroid Cancer B. January 2003 C. July 2005	A. Salivary Duct Carcinoma B. August 2016 C. March 2017	A. Secretory Carcinoma (Parotid) B. Fall 1998 C. No Metastatic Disease	A. Non-Small Cell Lung Cancer B. April 6, 2018 C. April 6, 2018
Where and how were you tested for Larotrectinib candidacy? Was there any cost to you?	**Foundation One Study** tested genetic makeup of tumour at MD Anderson. No cost to patients because insurance company picked up the $8000 fee. Deemed NTRK Gene Fusion Positive.	NGS on viable tumour sample performed at MD Anderson in December 2016 (NTRK3 Gene Fusion Positive)	NGS was performed on a LN that was discovered and removed from back of neck at MD Anderson in September 2018 at no cost. (**NTRK 3 Gene Fusion Positive**)	Genetic testing was performed on tumour slides from the original surgery on salivary gland at MD Anderson in April 2017. Tested NTRK Gene Fusion Positive.	Self-referral to MD Anderson in May 2018. Partial resection of primary tumour was performed in August 2017 and a sample was tested by MD Anderson in June 2018 for candidacy. No cost for testing. MD Anderson identified patient's tumour to be NTRK gene fusion positive.	Bronchoscopy was performed at Sanford Health in Sioux Falls on April 6, 2018. Sample was sent to Caris Life Sciences at no cost to the patient. NGS was performed which revealed PDL1 expression and some NTRK gene fusion activity. Not enough of a sample was provided to determine which NTRK gene fusion he tested positive. Another sample was sent to Caris in October 2018 when significant disease progression was detected. Once again, at no cost to the patient. NGS was repeated and on November 22, 2018 patient

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						was found to be NTRK 1 gene fusion positive.
Location of Metastatic disease?	Innumerable tumours in both Lungs, Neck, Soft tissue in thyroid bed	Lungs, Liver, Kidneys, and Multiple Lymph Nodes	Lungs, brain, jaw muscle, liver, gall bladder, LN back of neck, right armpit LN	Lungs, Lymph Nodes, base of skull and jaw.	No metastatic disease was detected.	Initially patient was diagnosed with brain, bone mets and 2 Lymph nodes under the right clavicle in addition to the diffuse disease in right lung. After disease progression in October 2018: liver, adrenal glands, pancreas, colon, pleura, diaphragm, right shoulder.
Therapies Received Prior to Larotrectinib for metastatic disease.	Phase I trial in August 2014 – August 2015. "Achieved only stability but horrible toxicity (nausea, diarrhea, body hair turned white, terrible skin irritation).	Multiple surgeries; 7 weeks of radiation on head and neck; Second round of radiation on head and neck	Radioactive iodine (2x); External beam radiation of the neck; Gamma knife for brain mets; Radiation for lung lesions	Surgery on salivary glands. 7 weeks of radiation on right side of face and neck.	Patient refused prior therapies except partial resection of primary tumour.	1. Keytruda + Carboplatin + Alimta 2. Radiation for brain mets 3. Taxol Significant progression detected in October 2018 which led to second sample testing.
When did you receive Larotrectinib and in what line of therapy? Date?	Second line therapy. Started in October 2015.	Started January 13, 2017 through a clinical trial (LOXO 101). First systemic therapy.	Started November 6, 2018 in first line therapy.	Late April 2017. First line therapy.	Started therapy in July 2018 and is still receiving Larotrectinib.	Started December 4, 2018 (LOXO 101)
How many cycles of Larotrectinib did you receive?	40 cycles	26 cycles	5 cycles	22 cycles	10 cycles	4 cycles
What side effects did you experience on Larotrectinib?	"I have no physical side effects from the drug. All I had were slightly elevated liver function tests (AST and ALT) for one month."	"The only minor side effect I have experienced is swelling in my ankles and withdrawal symptoms if I miss a dose. I	"I feel really lucky cuz I have very few to no side effects. 45 minutes after I dose, I have a feeling of overstimulation	"I experience some fatigue and withdrawal symptoms that consist of body aches, high sensitivity to light and my lungs feel as though they are	"My biggest side effect is a flu like symptom or body aches that's like withdrawal- like symptoms. As I approach the 12th hour before my second dose, I am not able to move well or stand very	"The only side effect I have experienced is ringing in my ears. That's it!! I walked 3 miles yesterday. Do you think I could have done that if I was experiencing side effects?"

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		take the drug twice every day (every 12 hours) so I experience withdrawal-like symptoms, such as leg cramping and tightness in my chest if I don't take the drug on time. But as soon as I take the drug, then I am back to normal and symptoms subside."	like too much coffee initially and then it settles down (a jittery feeling). 4 hours later, it's completely gone. There was this one time, where 10 days in, I had a skin sensitivity issue, where fabrics hurt my skin. It lasted only one week. both side effects have resolved completely."	expanding. I take my first dose at 6:45 a.m. and my withdrawal symptoms start at about 3:30 p.m. but as soon as I take my next dose at 5 p.m., the withdrawal symptoms dissipate completely approximately one hour later. These symptoms started about one year ago."	well, my muscles ache a bit and my body aches, but within 1-2 hours of taking the second pill in the day, I feel much better. The research says that it doesn't matter if you eat or not. But if I eat, my side effects are much less. Before and after taking my pill, I feel much better if I eat, the side effects are cut by 75%. So, eating before and after really helps. And I find that taking the second dose one hour earlier in the evening really helps a lot. The doctor has told me that the two doses must be 8 hours apart minimum. I didn't have any side effects till 5 months after starting the therapy. And I take a lot of supplements, such as liver and kidney clearance supplements, and Vitamins B and E."	
On a scale of 1-10, how would you rate your QoL while on Larotrectinib? 1 being very poor and 10 being very good. Why?	**10** "I have a very normal life on this drug. I have 3 children: two 5-year- old twins and a 19- month-old who keep me very active and busy. You would not know I even have	**10** "This is a fantastic drug. I have not missed a day of work since being on this drug. I am very socially active and do everything that I used to do before	**10** "For sure a 10. Very subtle inconvenience to my life – actually none. There's been no disruption to my life. I am so happy and grateful for this	**8** "I compare this therapy to other chemos that patients are on at the cancer centre and the radiation that I have been on and I believe this drug is pretty good in comparison. It's so much better	**9** "Except for having to time my outings accordingly, I have been really well on this drug. I tolerate the side effects pretty well and I figure it into my day to day schedule."	**10** "It's a ten definitely! I have my whole life back! I am no longer in a wheelchair or bedridden anymore, nor am I on oxygen anymore. It only took 4 days on this pill to get me off the oxygen. It was amazing."

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	stage IV cancer while being on this drug. I am able to conduct myself like a normal functioning member of society."	having been diagnosed with cancer. I just feel good! What can I say? "	drug and the effect to my life."	for me than the alternatives."		
Did you have any cancer symptoms before starting Larotrectinib? If so, what were they?	"No, none, other than the treatment induced side effects from the clinical trial I was on."	"Oh, yes. I had fatigue, tumour induced pain and incontinence! And for a business man, that s not a good thing as you can appreciate."	"Yes. For a year, I had a small bump on the upper part of my leg, and a knot on my calf muscle which gave me pain in my leg when driving. I had to stop driving altogether. Within a week of starting the drug, the pain and bump were gone. I felt it reduce in size and the knot in my leg was gone. No more pain!!"	"Yes, severe pain in my ear and jaw resulting from the residual disease (recurrence) from the salivary gland cancer. "	"Yes. I had horrible swelling over my facial tumour, more of a deformity from the primary tumour that could not be resected and I had neck discomfort and nerve pain. It was terrible."	"I sure did. I had tons of them because I was so close to dying. I had shortness of breath which is why I was on full time oxygen. I had headaches, dizziness, diarrhea, painful leg and arm blood clots, back pain due to the bone mets. I was being considered for admission to hospice care when I started this pill."
If you did have cancer symptoms before starting Larotrectinib, did your cancer symptoms resolve on Larotrectinib? If so, which ones?	**N/A**	"Yes, almost immediately! I could feel those tumours with my fingers but within 4-5 days on this drug, they resolved, and I could no longer feel them with my fingers. And the pain resolved	Please see above.	"Yes, the pain in my ear and jaw dissipated after the second cycle of Larotrectinib and it's never come back. "	"Yes! The swelling, neck discomfort and nerve pain are gone."	"All my cancer symptoms resolved a few days after starting this pill. I tell you, it's been a miracle pill for me. After only 4 days of taking LOXO, I was fully off oxygen, I was able to have a stat of 94-96%. After 5 days of being on the pill, I was no longer wheelchair bound, I could walk again."

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		as a result. The fatigue just vanished. I don't suffer from incontinence anymore."				
How was response confirmed to Larotrectinib: Clinically (symptoms resolved), biochemically , radiographically (CT)?	"CTs confirmed reduction of tumours in my lungs and my neck which have almost disappeared completely. I had a palpable mass on my neck. After the first cycle, I could no longer feel it. After the first cycle, CT showed reduction by 50%. "	"Yes, CT scans. When I first started the treatment, I had countless small tumours throughout my lymphatic system and then in my lungs, kidneys and liver. But after the first cycle, CT showed all tumours were gone except for one in my lungs that had shrunk by 65%!! And today there has not been evidence of a single new tumour and this last remaining tumour has shrunk by 90%. That's all the disease I have left. This is a wonder drug."	"Yes, through CT scans. After the second cycle, my tumours shrank by 34%. Now there are no new tumours."	"When I was at MD Anderson, I use to have PET/CT scans that would measure how I was responding to Larotrectinib. Then my insurance company said I had to switch over to CT scans alone. Regardless, I have had 85% shrinkage of my disease while being on this therapy."	"The August 2018 MRI, which was the first MRI showed a 30% reduction in the facial tumour. the second MRI showed a 68% reduction. The third MRI showed 70% reduction in the tumour. And this last MRI in February 2019 showed the tumour had completely disappeared! I am so blessed."	"At my 2 month scan, there was no active cancer left in my body!! Nothing is measurable anymore. My doctor says I have had a complete response to this drug. It really is a miracle."
Did you have to stop Larotrectinib? Why?	NO	"Not really. But, in April 2017, I had to undergo corrective surgery for scar tissue, so I had to stop therapy for **5 days**."	NO	"Yes, I was off this drug therapy for 3 weeks, in October 2018 because of an infection in my leg. The antibiotics I was taking were not compatible with the Larotrectinib, so I had to go off the drug. The infection had nothing to do with the Larotrectinib."	NO	NO

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Was it worth accessing Larotrectinib? Why or why not?	"Yes, absolutely. This drug changed my life. I would not be where I am today without this drug. It has no side effects for me and tolerating it is excellent. The oral drug is such a convenience! it's easy to administer at home as opposed to going to a cancer center every week or every other week, like I used to. I was not in a good place, I have to tell you, especially after that clinical trial but Loxo came at a good time for me has been a blessing and I needs to be a blessing for others too. I want to be a normal contributing citizen and live my life like everyone else, but I need to help others by participating in things like this. Others are struggling, I can see it when I go to the cancer centre. So, it's up to me to support them if I can both in the US and in Canada."	"Absolutely, I would be dead otherwise. The treatments I had before adversely affected my quality of life but this one has given me wonderful quality of life and this has not killed me. It has granted me what I believe is a wonderful cure.	"Yes. While my cancer was lurking around for 15 years, I can tell you that my cancer is now responding to this drug and without it, where would I be? I shudder to think about it. It's given me a new lease on life."	"Oh, ya. Cuz,. I'd be dead without it. Doctors at Emery in Atlanta had told me there was nothing for me and when I went to MD Anderson, they told me they didn't have anything for me too but they decided to send to clinical trials to see if something might be available, but warned me that if there was nothing available, I had less than 12 months to live. Imagine that, I was in my early 30s, and I was being told that I had less than 12 months to live. It was shocking. Here I am approximately 2 years later with 85% resolved disease! If it had been accessible to me earlier and not in the setting of a clinical trial, right from the beginning, then perhaps I could have accessed if and spared myself a fair amount of grief and avoided the metastatic journey and useless treatments like radiation. Who knows! "	"Sure it was. There is always collateral damage to accessing therapies like surgery and maybe more therapies like radiation. I should know cuz of what happed when I had the partial resection to my primary tumour. God only knows what would have happened if I had undergone the total resection of my primary tumour. it had wrapped itself around the facial nerve and if I had undergone a total resection, I would have experienced more trauma than I had. For example, inserting gold in the eyelid to open and close it, the cheek not working properly etc… Larotrectinib saved my life. I lost some of my sight with the partial resection. But if I had undergone total resection, I would have lost all of my sight and further traumatized the facial nerve. So this drug really has been a total blessing for me. And it's so easy to take, it's a pill twice a day - morning and night. So, yes, for sure it was definitely worth it to me."	"ABSOLUTELY! Because it's a life- changing miracle pill. We are so thankful that we found this mutation so that we can have our life back as a family. I have a wife and 2 young boys who depend on me. I am so happy I found this clinical trial. Or that it found me. It's been amazing. My boys are thankful for the pharma that made this drug and this response possible."
Did accessing Larotrectinib	**"YES, EVERYDAY!** When I was	"Yes, for sure. To be able to have a	"Yes. It has allowed me to	"Everything that I've done in the past 2	"The first thing I have	"Yes, I got to live instead of dying!! I get to go to my boy

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allow you to fulfill or accomplish anything that you would not have otherwise been able to, had you not accessed the therapy? If yes, please explain.	diagnosed, I ended up freezing my sperm because I didn't know what the cancer therapies would do to my sperm. Being on Loxo has allowed me to have my 19-month-old child!! There is no greater gift in life than to see the birth of your child. I am able to enjoy my 5-year-old twins every day and be a father to them as well in an active and loving manner as well as be a husband to my wife. I am living my life every day. No one would take me for stage IV cancer patient"	normal life and go to work, to the theatre, dinner, social events, charitable events, go to the gym, and go out with my partner is priceless! I feel like I am 16 again. I feel well on this treatment. It's not toxic. It does not interfere with my daily routine or my quality of life. And the fact that it's an oral treatment is a bonus, it's so easy that I can administer is myself. I don't have to go anywhere. How awesome."	continue to live my life with little to no toxicity, maintain the life I had before getting sick, travel with my husband, take care of my pets, work full time. I have a life without illness!! I participate in parades, such as Mardi Gras tomorrow. I lead a very active life, one which I didn't have before larotrectinib. I have gotten to do so many things that I would not have done had I not accessed this drug because I don't think I would be around today without it. That's the truth."	years in terms of being alive! I have 2 biological children who are 4 and 11 years old and I have 3 step children who are 5, 6 and 12 years old. They keep me young, active and mindful of how precious life is. I am able to do things with them every day because of this drug. I am a college football fan, so we go to games all the time. We go camping all the time. We live life as a family to the fullest."	been able to do is **FEEL BETTER**, that I can tell you without I doubt. I know this 100%. My tumour was growing so aggressively in the last year and I know I wouldn't be here today were it not for this drug nor would I be feeling as well as I am. My outlook on life is so much better and I am able to go RVing because of it. I no longer take heavy pain meds because of the response I have had to this treatment. It's made a huge difference."	Nathan's basketball games and to my other boy Gavin's soccer games. And I get to be a husband to my wife Jennifer. Isn't that what it's all about? Family, spending time together, making memories, going out for dinner, laughing, helping the kids with their homework. I couldn't have asked for more."
Do you wish to add anything about why accessing Larotrectinib is so important to patients and caregivers?	"This is a life changing breakthrough drug. Anyone that has the mutation should be given the opportunity to have the life changing experience that I	"The sooner you can test patients, the better to avoid toxicity and discomfort. I would recommend getting on this drug as soon as possible if you qualify. Please fund this drug for patients like me who	"Even though this drug impacts a small group of people, the impact it has, the ripple effect is so enormous and profound! The impact is far reaching –	"The NTRK gene fusion that this drug treats is found commonly in rare cancers but rarely in common cancers. So, people who have rare cancers like me, don't have access to therapies that treat rare cancers	"It's common sense to approve this drug. I don't think about my cancer anymore others should be given this privilege too. Life is much more carefree. My jaw doesn't hurt anymore. My quality of life is much better because of this drug. That's	"I want Canadians to have the opportunity to live much like I have had the opportunity to live by accessing this pill which will allow them to beat cancer. This pill is truly a miracle because we did not have a funeral before Christmas. Instead, we now are waiting for the summer to have a family

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	have had (both in the US and in Canada). No patient should be denied. I hope your government approves it. I am living proof of why they should."	have a cancer that has a mutation that can be targeted. This drug has a different approach to treating cancer. Because of accessing this drug, I am a productive member of society and I have been spared a horrible fate. This drug won't be killing patients or allowing them to suffer. Instead, it will be helping them in a less toxic manner and more targeted fashion. Patients and their families deserve to have it."	socially, economically, emotionally, psychologically on the family, the work environment, the patient themselves and so much more. This is the first drug that is testing multiple cancer sites and has potential benefit for so many cancer patients and their families and can do so much good. Everyone in the cancer community has a responsibility to ensure this drug becomes available to patients who qualify for it after proper testing."	effectively. People who have cancers that are responsive to typical therapies are ok but people like me need this drug therapy to survive. Patients like me can skip useless treatments and proceed directly to effective therapies like larotrectinib and avoid useless treatments that are ineffective, like the radiation that I was on. Please fund this treatment for the patients who desperately need it."	huge for me. No more pain meds! How can you not want this for Canadian patients? You should, if they have TRK receptors and if they are properly monitored, why not fund this drug? It would be a terrible injustice to not make it available to them. I feel joy every day and gratitude because of this therapy. I have life so easy compared to others and yet it's been so hard. I know firsthand how difficult the journey has been and Larotrectinib has made it better. Collateral damage has been ameliorated by this drug. You all have the opportunity for this amelioration. I hope you take advantage of it. Your patients who quality, deserve it, especially for the convenience. It's a no brainer. There's a History to support it already, historical baseline already. Please fund it."	vacation. None of it would have been possible with this drug. Those who qualify deserve to get it like I have gotten it so they can have their second chance. Please give it to them."

CCC indicated that it was unable to interview a colorectal cancer patient who had experience with the therapy under review. However, given that the therapy under review is a cancer drug that treats tumours based on the genetic properties of that tumour, rather than their site of origin in the body, CCC felt confident in having secured the perspective of six non-colorectal cancer patients representing four different cancer disease sites. CCC believes this new site-agnostic cancer therapy is not specific to a cancer that arises in a particular body organ – as such, the tumour's tissue of origin is therefore not clinically relevant. Instead, the presence of a specific genetic tumour biomarker (rather than the site at which the cancer originates) is of paramount importance and unites the various disease sites containing the genetic mutation. CCC noted that patient respondents cited the following treatment-induced side effects: elevated ALT/AST levels, tinnitus, swollen ankles, withdrawal-like symptoms, overstimulation, fatigue, sensitivity to light, and flu-like symptoms – all of which were considered by patients to be tolerable/relatively minor. According to the patient respondents, this treatment has delivered a clinically meaningful response in their cancer that has been identified to be TRK gene fusion positive. Their disease has either resolved completely, significantly or to a great extent, while managing to maintain the highest level of quality of life. For those patients who were experiencing cancer-induced symptoms prior to starting Larotrectinib, all reported a significant improvement in those symptoms after starting the therapy. No patient experienced a treatment interruption due to treatment-induced toxicity and efficacy was radiographically confirmed in each patient through CT. Additionally, all patient respondents appreciate an easily administered oral therapy in the comfort of their homes. It is important to note that Patient 1 was able to go on to have a child and enjoy his 5-year-old twins. Patient 2 has resumed a normal active life, feeling so well, as though he is 16 years old again. Patient 3 reported feeling as though she has no illness on larotrectinib. Patient 4 enjoys his five children every day who keep him young. Patient 5 feels better than she has ever felt now that she is on the therapy under review. Patient 6 is no longer in need of hospice care after having had a complete response to larotrectinib.

LCC reported on five patient respondents who had experience with larotrectinib. The first patient respondent noted that the tumor occupied 90 percent of her lungs; she was on oxygen and in a wheelchair. After genomic testing and looking for options, she was placed on larotrectinib. Four weeks after beginning treatment, she was able to take her kids the movies and even celebrate her birthday. This patient respondent progressed on chemotherapy, despite several rounds. When her cancer spread she thought she would have to give up as she had received several cycles and it seemed there was no other course of treatment available. After her genomic testing showed she had the NTRK gene fusion and there was a targeted treatment available, it was such a relief, it gave her hope again and she didn't have to give up. The targeted therapy has allowed this patient respondent to celebrate milestones with her family. Now she looks forward to knitting and going on vacation.

A second patient respondent was given 3 to 4 weeks to live. His genomic testing showed he had the NTRK gene and his oncologist enrolled him in a clinical trial for larotrectinib. For this patient respondent, it seemed like a rollercoaster, one moment he was told he was going to die, his family was worried about losing him, and the next there was a new drug that could save his life and save his life it did. Four days after receiving treatment he stated that he was already feeling better and his symptoms including pain, fatigue, weight loss, incontinence improved. The first scan after four weeks of treatment showed all the tumors in his body were gone and 65% of the tumor in his lungs had disappeared. He is currently stable, has gained his weight back and has been on larotrectinib for two years. The patient respondent has not missed work because of treatment with larotrectinib and only complained of slight ankle swelling. His family is absolutely thrilled, and he is happy

to be alive right now and on a treatment that not only saved his life but allows him a quality of life that does not keep him in bed or interfere with his health or activity, but rather allows him to be free to work, walk around and even go to the gym every day.

A third patient respondent reported that within 72 hours of treatment, he no longer needed a cane; and within two weeks, he was walking around the city, playing with his kids and eating like a champ.

A fourth patient respondent stated that chemotherapy did not work but since treatment with larotrectinib, she currently has no evidence of disease. This patient respondent also reported that she preferred the oral administration of the treatment and said she had fewer side effects compared with chemotherapy. The treatment did not make her as sick compared to when she was on chemotherapy.

A fifth patient respondent diagnosed with stage 4 NTRK positive lung cancer two years ago reported that he is currently stable and still able to work as a high school basketball coach and has even had a championship season and his 400th win. The respondent says, "*The hope for my mutation - we can turn this into a treatable, chronic disease versus what it's been, which is the No. 1 killer of all the cancers out there*".

NC conducted an interview with the parents of a child taking larotrectinib. The patient respondent was on an elite soccer team prior to being diagnosed with thyroid cancer. At the age of 12, he came to his parents noticing that he had a lump on the right side. His parents took him to the walk-in clinic and thought it was unusual. He went to see an oncologist and endocrinologist and was operated on within a week and had the lump removed. The family had all of the risks explained to them about the challenges of the surgery. After the first surgery, he also had a small amount of radiation and thought that they were good and would just have endocrine appointments as he no longer had a thyroid. He would undergo blood work on a regular basis. Almost a year later, his testing came back saying that he still had cancer. He had to go back and do a second surgery to remove the cancer. The second surgery was much harder on him. He was going into grade 8 and was self-conscious about the scar. He was no longer playing soccer since he didn't have the endurance. He had to do more radiation after the second surgery. He was taking medication for his thyroid. It was harder for him to get back into routine; he stopped playing sports and he stopped associating with many of his friends as he didn't want to answer questions about his treatment. According to his parents, he kept everything inside and didn't want to explain to people what was happening to him. It was more challenging the second time around; he gained weight and didn't go to school and experienced depression. He did a lot of research on his own about what foods to eat and not eat. He started to lose weight, and this has helped his self-esteem. His parents noted that dealing with cancer during the teenage years is very challenging because they are robbed of their formative years. His physician did the genomic analysis through POG on the tumour to find the NTRK mutation and he was presented the opportunity of taking larotrectinib. He receives treatment from Seattle where the study is being run. The tumour has shrunk since being on treatment. It is still a little difficult to tell at this time if it is scar tissue or disease since they can't do a biopsy at this time. The parents reported that he hasn't really had any side-effects. His body tells him when it is time to take the medication as he gets a few aches. It is an oral capsule that he takes in the morning and night (twice a day). He doesn't like the fact that he has to take the medication. His parents found that it is a huge difference in terms of his quality of life. With radiation, he can't be around anyone. With larotrectinib, he can go out and do things and be with people; whereas, with radiation he was very sheltered, it was a psychological burden. He can take his pills with him to go places, he can live his life. There is no hospital stay, which is huge. There are

no scars. The past three years have been a big difference; 32 months on the larotrectinib so far. He has a job and has his own car and has a small circle of friends. The parents reported that it has been a very difficult five years. You can spend 3 hours driving for a 30-minute appointment and out-of-pocket expenses. The parents noted that it is emotionally draining. You see your child go through so many different challenges and sometimes you can only watch them go down the rabbit hole. You want them to be kids and have that chance at life. The parents indicated that making decisions about a new treatment means quality of life, how he feels and how he adapts to it. It is all about him, his well-being, his life and longevity. These decisions are hard to make as a teenager.

The patients with whom SCFC spoke with were several years beyond their treatment and had not experienced any disease regression or reappearance of tumours. Both patient respondents accessed larotrectinib via clinical trial. One patient respondent described being unable to move, confined to a wheelchair and going from stage 4 inoperable tumours to disease free and able to return to his career in his physical job as a police officer while completing a 350-mile bike ride. The patient respondent described going from being unable to leave the house due to vomiting and pain and virtually unable to walk to being asked to join an elite physically demanding law enforcement team, also becoming the father of twins. The patient respondents reported no side effects of treatment and were amazed at the speed with which the treatment began to work. Patient respondents described the radical transformations with the use of larotrectinib, resulting in quick and effective treatment. SCFC submitted this type of result is extremely uncommon among existing non-surgical treatments. Patient respondents described being "*on death's door*", confined to a wheelchair, unable to breathe, on as many as 5 litres of oxygen per hour, barely coherent, and headed for hospice care, to a completely disease-free return to normal activities like horseback riding and marathon running within a matter of weeks. These two patient respondents are now a number of years out from their initial treatment with no discernable side effects. SCFC also indicated that caregivers described a radical change from a person being near death to anticipating many long years together. The caregivers themselves have also been able to return to normal life and did not experience lengthy, protracted periods of overseeing treatment as larotrectinib had relatively fast results for the patient respondents who were interviewed.

All six patients interviewed by CCC confirmed they tested positive for the unique biomarker, the NTRK gene fusion. Five patients were tested at MD Anderson and one was tested through Avera Treatment Centre, at no cost to them. Patient respondents were grateful to have been identified and enrolled into the clinical trial for they all had tumours that had metastasized or could not be surgically removed and had progressed during previous treatments. None of the patient respondents expressed concern or difficulty having accessed the testing centre. The out of town patient respondents maintained it was well worth having travelled the distance to access the biomarker test and the clinical trial, for it has either saved or prolonged their life. According to CCC, this clearly underscores the need to conduct upfront next generation sequencing testing in the metastatic population. While NTRK-gene fusions are rare in sporadic colorectal cancers (1-2%), this alteration is more common in colorectal tumours deficient in mismatch repair (dMMR), and tumours with high levels of microsatellite instability (MSI-H). Colorectal cancer patients who are identified to be MSI-H and with metastatic disease, should undergo upfront next generation sequencing testing, which includes testing for the NTRK gene fusion biomarker. LCC noted that diagnostic testing for the NTRK gene fusion is currently not available or funded in Canada. With the increasing importance of genomic profile testing and personalized medicine, this form of testing is needed. SCFC also noted that patient respondents were proponents of these tests being made widely available.

CCSN asked patient respondents on the expectations they had for their long-term health and well-being as a result of taking larotrectinib; patient respondents reported the following:

- Salivary Duct Patient 2: "*As long as my body has good responses I will live*."
- Parotid Gland Patient 5: "*Continued reduction of tumour size*"
- Thyroid Patient 1: "*I hope to have continued success. I hope to have no evidence of disease and to remain that way for a very long time*."

Thyroid Patient 3: "*My long term outlook has completely changed because of the larotrectinib. I expect to continue treatment and enjoy my daily life in my career and with my family because of this drug*."

3.3 Additional Information

CCC submits this targeted therapy, agnostic to a tumour's tissue of origin, is a demonstration of precision medicine and evidenced that the right patients can receive the right treatment at the right time based on a patient's tumour genetic profile. Funding a molecularly targeted therapeutic that treats patients with an array of cancer types based on the presence of a specific tumour biomarker rather than the site at which the cancer originates, aligns well with the patient perspectives captured within this submission. If publicly funded, patient groups collaborating on this submission feel that larotrectinib could be an extremely important therapeutic option for cancer patients (including colorectal cancer) whose tumours test positive for an NTRK gene fusion, are metastatic, where surgical resection is unlikely, or have progressed following treatment.

LCC noted that due to the rarity of this mutation, this submission was made using Phase 2 data – a phase 3 trial would be extremely challenging, and one is not planned. LCC acknowledges that that pCODR (pERC) will find uncertainty in the current available data. In light of this, LCC hopes that pCODR will consider issuing a positive recommendation conditional upon the collection of additional data. In the case of lung cancer, BC and AB have patient registries. An interprovincial registry is also being planned so there is a credible method for the collection of RWE. LCC understands that other cancer disease sites also have registries as well. LCC also recognizes that the cost of this treatment is very high. US news reports suggest that it may be $32,000 US/month for adult dosing. Our public healthcare system cannot afford this price. LCC, therefore, recommends the manufacturer work together with payers to come up with sustainable pricing solutions so Canadians can gain the life possible with targeted therapies.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from **all nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Place in therapy for larotrectinib

Economic factors:

- Additional health care resources may be required to monitor and treat toxicities
- Number of patients requiring and access to NTRK gene fusion testing

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that there is no standard of care for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumors harboring a NTRK gene fusion. Treatment is dependent on the specific type of solid tumor, clinical trials may be offered to patients harboring a NTRK gene fusion. For patients who have progressed on all available treatment options, best supportive care would be available.

4.2 Eligible Patient Population

The three pivotal trials of larotrectinib are a phase I study in adult patients with solid tumors, the SCOUT trial in advanced pediatric solid or primary CNS tumors, and the NAVIGTATE trial in patients with NTRK fusion positive solid tumors. PAG noted that these trials included patients with an ECOG 0-2, Lansky Performance Score (LPS) >40%, or Karnofsky Performance Score (KPS) >50%. PAG is seeking guidance on the use of larotrectinib in patients with poor performance status (i.e., ECOG >2, LPS <40%, and KPS <50%).

If recommended for reimbursement, PAG noted that patients that are identified to harbor a NTRK gene fusion and currently on other treatments, would need to be addressed on a time-limited basis.

4.3 Implementation Factors

Depending on other treatment options, larotrectinib may be associated with less chair time which would be an enabler to implementation. Larotrectinib is available as a capsule or oral solution formulation. PAG noted that the oral solution formulation, especially for pediatric patients or those unable to take the capsule form, would be an enabler to implementation. However, dispensing larotrectinib would require additional pharmacy resources.

Additional health care resources (e.g., frequent clinic visits while patients are on therapy) are required for monitoring adverse effects and tolerability with larotrectinib.

Larotrectinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on larotrectinib's place in therapy. PAG is seeking guidance on the appropriate treatment options for patients with locally advanced or metastatic solid tumors harboring a NTRK gene fusion,

- What is the optimal sequencing of larotrectinib with other treatment options (i.e., would use be after all other treatment options are exhausted)?
- What would patients receive after progression on larotrectinib?

4.5 Companion Diagnostic Testing

PAG noted that NTRK gene fusion testing is not routinely available in all provinces. Jurisdictions do not currently have testing for NTRK gene fusion available in their provinces, and other options, such as sending tissue samples out of province, would need to be explored. As there is no formalized testing process or funding in place for NTRK gene fusion testing in jurisdictions, this would be a barrier to implementation. Health care resources and coordination to conduct NTRK gene fusion testing will also be required. The increase in costs for NTRK gene fusion testing is a barrier to implementation.

PAG had concerns related to:

- The turnaround time for NTRK gene fusion testing
- Guidelines on criteria for testing and whether all patients should be tested
- Expected number of patients eligible for larotrectinib (i.e., anticipated number of patients requiring testing per year, with tumors harboring a NTRK gene fusion, and who would receive larotrectinib treatment)
- Timing of testing and whether patients should be tested at diagnosis or at relapse

Therefore, the number of patients requiring and access to NTRK gene fusion testing may be a barrier to implementation.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Five clinician inputs were received for the pCODR review of larotrectinib for solid tumours harbouring a NTRK gene fusion. There was one single clinician input, and four joint clinician inputs comprising of 26 oncologists and one pharmacist from the following groups: Colorectal Cancer Canada (CCC; 11 clinicians), the Pediatric Oncology Group of Ontario (POGO; five clinicians), Lung Cancer Canada (LCC; seven clinicians), and Cancer Care Ontario (CCO; three clinicians and one pharmacist). The single clinician input provided input in regards to thyroid, lung, and head and neck cancers. In total, input was received from 27 oncologists and one pharmacist.

All clinicians agreed that patients eligible for larotrectinib would need to present with solid tumours harbouring the NTRK gene fusion. Ideally identification of the NTRK gene fusion would occur during diagnosis of the patient's tumour, or during testing for other mutations. While identification of the NTRK gene fusion is a requirement for patients to receive larotrectinib, it was identified that there is no routine testing for NTRK currently available, and that testing is not funded. However, a number of tests to identify the NTRK gene fusion were stated, including immunohistochemistry, fluorescent in situ hybridization (FISH), nanostring technologies, next generation sequencing, biopsy or fine needle aspiration cytology (FNAC). None of the clinicians had any experience using larotrectinib, as the clinical trials for the drug were not open in Canada. However, compared to other therapies, such as cytotoxic chemotherapy, larotrectinib was stated to show greater efficacy and a favourable toxicity profile. According to the clinicians providing input, the use of larotrectinib in a specific line of therapy was dependent on the type of cancer being considered.

It was stated in the joint input from the clinicians from CCO that there was not sufficient evidence to identify an unmet need for breast cancer patients at this time. Therefore, larotrectinib was given a low priority by CCO for patients with breast cancer. Alternatively, POGO, LCC, CCO and the single clinician stated that larotrectinib would be useful to patients as it is tolerable, easy to administer as it is an orally administered therapy, and efficacious.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for Solid Tumours harbouring a NTRK gene fusion

Table 5.1 includes treatment options available for patients as stated in the joint submission from CCC.

POGO stated that there were no funded or endorsed treatment strategies in Ontario for the small subset of pediatric malignancies harbouring the NTRK gene fusion. However, conventional cytotoxic agents are used to treat a variety of the pediatric tumours harbouring the NTRK gene fusion; although, these are funded out of the local Hospital Global Budgets.

As stated by LCC, combination cytotoxic chemotherapy regimens were highlighted as a general comparator. Regarding non-small cell lung cancer (NSCLC), the LCC clinicians noted chemotherapy and immunotherapy; specifically, they highlighted immunotherapies as options for patients with PD-L1 positive tumours in the first line, and as an option for patients in the second-line regardless of PD-L1 status. The immunotherapies were stated to have fewer side effects and lead to better quality of life compared to cytotoxic chemotherapy. The LCC clinicians stated that the effects of immunotherapies are blunted by tumours driven by certain key mutations, which include the NTRK gene fusion. They added that regardless of PD-L1 status, most oncologists would be very reluctant to recommend immunotherapy as first-line treatment to NTRK positive lung cancer patients.

The single clinician input indicated that provincial funding is currently available for patient with locally advanced or metastatic, radioiodine-refractory (RAIR) differentiated thyroid cancer (DTC) to participate in a trial of lenvatinib, which has shown to improve progression-free survival and response rates. The single clinician stated that other drugs do not provide benefits as significant as lenvatinib in this setting. However, after one to three years of receiving lenvatinib, patients will develop progression upon which there are no good standard treatments.

No treatments currently available for NTRK-positive breast cancer patients were identified by CCO.

Table 5.1: Current treatment patterns for patients with colorectal cancer, chlorangiocarcinoma, GIST, pancreatic cancer and hepatocellular carcinoma

	Line of therapy			
Indication	**First**	**Second**	**Third**	**Fourth**
Colorectal cancer	FOLFOX, FOLFIRI +/- bevacizumab, EGFR inhibitor (if RAS wild type and contraindication to bevacizumab)	FOLFIRI or FOLFOX	For RAS wild type: panitumumab or cetuximab +/- irinotecan For RAS mutated: regorafenib or TAS-102 if available	Regorafenib or TAS-102 if available
Chlorangiocarcinoma	Gemcitabine, cisplatin*			
GIST	Imatinib*	Sunitinib**	Regorafenib**	
Pancreas	FOLFIRINOX or gemcitabine/nab-paclitaxel	Gemcitabine +/- nab-paclitaxel (if not received in first line) or irinotecan based treatment if received FOLFIRINOX		
HCC	Sorafenib or lenvatinib	Regorafenib or cabozantinib		
Abbreviations: GIST=gastrointestinal stromal tumours; HCC=hepatocellular carcinoma *for treatment of either locally advanced or metastatic disease **for treatment of advanced or metastatic disease				

5.2 Eligible Patient Population

The CCC clinicians stated that patients with advanced colorectal cancer, chlorangiocarcinoma and gastrointestinal stromal cancers do not have their tumours tested for the presence of a NTRK gene fusion as no prior treatment targeting the NTRK biomarker was available.

All clinician providing input agreed that eligible patients would be those with tumours harbouring a NTRK gene fusion. CCC stated that larotrectinib could be provided to patients in first, second, third or fourth line as long as patients are eligible in terms of performance status, organ function, etc. The POGO clinicians specified that larotrectinib should be prioritized for patients who have known metastatic/poor prognosis malignancies with existing chemotherapy and radiation therapy, have resectable tumours and have failed low intensity therapies aimed at facilitating surgical resection, and who have relapsed following front-line therapy. They also stated that NTRK gene fusions are found across a wide variety of pathologies and that they endorse the approach of focusing on the presence of the target rather than the specific histology.

It was stated in the single clinician input that larotrectinib could be suitable for patients with locally advanced or metastatic thyroid cancers with tumours harbouring a NTRK gene fusion, especially of RAIR DTC, and for patients with locally advanced or metastatic lung tumours harbouring a NTRK gene fusion. The LCC clinicians acknowledged that patients with NTRK positivity account for less than 0.5% of NSCLC patients. Lung cancer patients eligible for larotrectinib would have to be NTRK positive and closely resemble the study populations in the existing early clinical trials. It was stated in the joint clinician input from LCC that cytotoxic chemotherapy and immunotherapy were not as effective for lung cancer patients; therefore, there is an unmet need for treatment for these patients. The LCC clinicians also stated that, due to the small number of lung cancer patients with NTRK positive tumours, large randomized controlled trials including these patients are unlikely to be conducted.

The CCO clinicians stated that breast cancer patients were not applicable

5.3 Relevance to Clinical Practice

It was stated in the CCC joint clinician input that there was no clinical experience with larotrectinib in the Canadian adult oncology setting, as the larotrectinib clinical trial were not open in Canada. For patients with colorectal, pancreas or cholangiocarcinomas, larotrectinib would be a significant improvement beyond current standard options given the route of administration and lack of chemotherapy related toxicity. Sunitinib, imatinib and regorafenib are currently available treatments for GIST patients; larotrectinib would be an additional treatment option. For patients with hepatocellular carcinoma (HCC), currently funded options include sorafenib and regorafenib while other treatments are being reviewed. The CCC clinicians stated that while experience with larotrectinib is limited, its safety profile has been demonstrated to be favourable. The inputs received from POGO and the single clinician commented on the safety of larotrectinib. The POGO clinicians stated that larotrectinib is safe, well tolerated and less toxic than traditional high intensity cytotoxic chemotherapy. The single clinician input stated that the safety profile of larotrectinib is “very good”, specifically in comparison to lenvatinib for RAIR differentiated thyroid cancer. The LCC clinicians stated that larotrectinib showed similar efficacy across a broad range of histologies (almost 20) in the presence of the NTRK translocation. They also commented on the tolerability or larotrectinib. The trial included patients ranging from infancy to late adulthood, and with ECOG performance status of 3. Tolerability and duration of disease control were stated to be remarkable across the board, showing superiority over cytotoxic chemotherapy regimens and immunotherapy, which can be associated with significant immune mediated adverse events. In addition, immunotherapies are less effective against mutation driven cancers, such as EGFR, ROS-1 and ALK. The clinicians also noted that checkpoint blockade inhibition was shown to be associated with worse prognosis in driver mutation dependent cancers despite high expression of PD-L1; therefore, oncologists would have reservations about offering immunotherapy to NTRK patients compared to larotrectinib.

It was further stated in the joint input from LCC clinicians that larotrectinib would serve as a more attractive option for patients with co-morbidities, as cytotoxic chemotherapy is contraindicated in frailer patients with advanced disease. Larotrectinib was stated to be feasible for patients with an ECOG status of 1 or 2 with NTRK positive tumours.

Table 5.2 presents the comments by the POGO clinicians on the use of larotrectinib in pediatric cancers.

The CCO clinicians stated that a phase I study with one breast cancer patients is insufficient evidence to extrapolate the use of larotrectinib to breast cancer patients. In addition, there is

no unmet need for these patients as NTRK-positive tumours for breast cancer have not yet been characterized well enough.

The single clinician input stated that potentially eligible patients, for larotrectinib require a biopsy or FNAC of the progressive tumour site. The clinician highlighted that the cost for this analysis is approximately $700 CAD. If the tumour is found to harbour the NTRK gene fusion, the patient would be assessed by the team's medical oncologist for treatment with larotrectinib.

Table 5.2: Larotrectinib in clinical practice among pediatric patients, based on the joint clinician input from POGO

High frequency TRK fusion harbouring pathologies	These include Infantile Fibrosarcoma (IFS), Cellular congenital mesoblastic nephroma (CMN), secretory breast cancer (SBC) and mammary analog secretory carcinoma of the salivary gland (MASC)
	The upfront therapy of choice for these patients remains surgical resection, however for many it is not feasible without significant morbidity
	These patients should be considered candidates for larotrectinib if low intensity/low toxicity cytotoxic therapy (such as vincristine and dactinomycin) are not sufficient to control disease and allow resection. Larotrectinib should be prioritized over traditional cytotoxic agents with higher potential late effects such as anthracyclines or alkylators.
Lower frequency TRK fusion harbouring pathologies	In diagnoses with known poor prognoses (i.e., high grade gliomas, metastatic sarcoma, metastatic papillary thyroid cancer) larotrectinib therapy should be considered as part of front-line therapy. Patients with stable disease or significant responses should be funded to continue on therapy until either a complete response is achieved or they show evidence of progressive disease.
	In diagnoses with good prognoses, larotrectinib therapy should be reserved as a second-line therapy until evidence showing equivalent or better than current front-line therapy is available.

5.4 Sequencing and Priority of Treatments with Larotrectinib

The CCC clinicians provided the following sequencing for colorectal cancer, cholangiocarcinoma, GIST, pancreatic cancer and HCC:

- For colorectal cancer, larotrectinib may be given in the first, second, third or fourth line
- For cholangiocarcinoma, larotrectinib may be given in the first line setting, replacing gemcitabine and cisplatin, or in the second-line setting.
- For GIST, larotrectinib may be given in the second-line setting, replacing sunitinib, third-line setting, replacing regorafenib, or fourth line setting.
- For pancreatic cancer, larotrectinib may be given in the first or second-line.
- For HCC, larotrectinib may be given in the first, second or third-line.

From the single clinician input, treatment sequencing for metastatic DTC was provided as follows: systemic therapy with radioiodine would be provided as first-line therapy up to a maximum dose of 600-800 mCi. Once the maximum dose is reached or considered RAIR, lenvatinib would be considered as second-line therapy for eligible patients (those without

comorbidities or pre-existing hypertension). Larotrectinib may be offered to patients as a final line of therapy if they are found to be NTRK positive.

Input from LCC stated that, based on clinical practice, larotrectinib would be used in the first-line setting among patients with NSCLC harbouring the NTRK gene fusion. Therefore, chemotherapy would be pushed to second or third-line, with the expectation of second and third generation NTRK inhibitors becoming available as resistance to larotrectinib develops. Immunotherapy would be offered only after chemotherapy fails.

The CCO clinicians stated that sequencing and priority of treatments were not applicable to breast cancer patients.

5.5 Companion Diagnostic Testing

The clinicians providing input noted that testing for this gene fusion would ideally occur at the same time as testing for other mutations such as RAS, RAF, and MSI for those with colorectal cancer. The CCC clinicians highlighted that HCC, cholangiocarcinoma, gastrointestinal stromal tumours (GISTs), and pancreatic cancers are not associated with genomic profiling.

The CCO clinicians stated that NTRK testing is required for larotrectinib, and that Ontario has the capacity to perform this test. However, there is currently no routine testing for NTRK available, and NTRK testing is currently not publicly funded. The LCC clinicians added that while testing is currently unavailable and not funded in Canada, two promising trends indicate the increased availability of NTRK testing over the next five years: the increasing number of targeted therapies, and the declining cost of next generation sequencing testing.

The joint clinician input form CCC stated that NTRK testing is currently in the gene panels for the solid tumour Foundation One and OCTANE clinical study. In British Columbia, NTRK testing is being added to the OncoPanel, which is used in colorectal cancer, and needs director's approval for other non-approved tumour sites or genomic clinical trials (POG, personalized oncogenomics).

The POGO clinicians identified the following 'standard of care' assessments for pediatric patients: immunohistochemistry, fluorescent in situ hybridization (FISH) for particular translocations and/or nanostring technologies. These assessments are particularly important for high frequency TRK fusion pathologies (i.e., IFS, CMN, SBC, MASC). The POGO clinicians identified that Next Generation Sequencing of tumours in accredited labs is at present limited to high risk or relapsed tumours and is currently assessed through research funded by philanthropic funds. The joint clinician input form LCC also identified next generation sequencing and FISH.

For locally advanced or metastatic DTC, the single clinician stated that assessment of NTRK gene fusion is performed via biopsy or FNAC of the progressive tumour site.

5.6 Implementation Questions

5.6.1 In regard to question 3.4 above, please consider the optimal sequencing of larotrectinib with other treatment options for adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a NTRK gene fusion.

5.6.1.1 In clinical practice, if larotrectinib was available, would your preference be to use larotrectinib in the first-line setting or reserve larotrectinib after all other treatment options are exhausted?

Based on input from the CCC clinicians, larotrectinib would be the preferred treatment in the first-line or later setting for colorectal cancer, cholangiocarcinoma, pancreatic cancer and HCC. Larotrectinib would be the preferred treatment in the second-line or later for GIST.

It was stated in the POGO joint input that clinicians would prefer to use larotrectinib as part of first-line therapy for pediatric patients, and that clinicians endorse the use of larotrectinib as part of earlier lines of therapy in general. The LCC clinicians also stated that larotrectinib would be the preferred first-line treatment for NTRK positive cases, as it is more tolerable and shows greater efficacy than cytotoxic chemotherapy and immunotherapy.

The single clinician input that concerned thyroid, lung, and head and neck cancers stated that larotrectinib would be a therapy used in later lines of treatment, possibly as a final line of therapy.

The joint clinician input from LCC provided additional comments regarding the price of larotrectinib, acknowledging the high cost of larotrectinib and the unsustainability of high cost drugs funded by the Canadian public health care system. LCC would support a recommendation conditional on improved cost of larotrectinib to a more supportable level. Real world evidence currently being accumulated by provincial databases, such as the Glans-Look, or national registries were identified by LCC as being tools to help adopt larotrectinib into clinical practice.

5.6.2 In what clinical scenarios would larotrectinib be the preferred treatment for adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a NTRK gene fusion? Please comment on the preference considering patient preference, efficacy, safety, and administration.

The CCC clinicians stated that, in general, patients prefer oral treatments over treatments that are intravenously administered. Patients also prefer targeted therapies compared to conventional chemotherapy. Among patients with contraindications, including known dihydropyrimidine dehydrogenase (DPD) deficiency, coronary vasospasm to 5-FU, or hearing loss, larotrectinib would be preferential. POGO once again indicated that larotrectinib would be the preferred treatment during earlier lines of therapy. The clinicians providing input from POGO and LCC highlighted that larotrectinib is better tolerated and less toxic than chemotherapy.

Similar to the joint input from CCC, the LCC clinicians stated that orally administered treatments show better compliance among patients. In addition, the improved efficacy and tolerability of larotrectinib may be associated with improved quality of life and better outcomes. Therefore, LCC would prefer to use larotrectinib among patients with solid tumours harbouring a TRK fusion when the alternative treatment options are cytotoxic chemotherapy, immune therapy or no treatment at all.

The single clinician input stated that if patients with locally advanced or metastatic DTC are considered to be RAIR and have significant co-morbidities or pre-existing hypertension, their tumours should be tested for NTRK gene fusion and considered for larotrectinib, instead of lenvatinib.

Please refer to section 5.4 for more information.

5.6.3 With respect to NTRK gene fusion testing, how are patients currently being tested? Should all adult and pediatric patients with locally advanced or metastatic solid tumours be tested, or should testing be limited to patients with specific types of solid tumours (if so, what types of tumours)? Should testing be available at all cancer centres? When should testing be completed (i.e., at diagnosis or at time of relapse)?

The LCC clinicians identified that there is no current standard testing algorithm for NTRK testing in Canada, although the capability for testing does exist in many centres. The CCC clinicians stated that the NTRK testing is currently performed for patients who have their tumours analyzed using a comprehensive tumour gene panel, such as the Foundation One. The POGO clinicians stated that for histologies with known high frequencies of TRK fusions, assessment should be considered in the front line as a standard of care for diagnoses. Some tests for assessment were stated to be immunohistochemical, FISH and/or nanostring. It was also stated in the POGO joint clinician input that Next Generation Sequencing should be considered for patients with high risk malignancies, including those presenting with either metastatic disease or recurrent disease. However, Next Generation Sequencing is not a currently funded test.

The CCO clinicians stated that testing for NTRK gene fusion should be limited to patients with specific types of solid tumours who are metastatic, where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment. The CCC clinicians stated that testing for NTRK gene fusion should be performed on patients with advanced colorectal, cholangiocarcinoma, pancreas, HCC and GIST tumours as part of a comprehensive gene panel. For patients who have had surgery, testing for NTRK gene fusion would occur at the time of disease recurrence. For patients with locally advanced or metastatic disease, testing for NTRK gene fusion would occur at time of consideration of treatment for advanced disease. It was stated in the joint clinician input from LCC that a logical approach to begin testing patients is to align with patients best represented in early phase trials; although LCC does acknowledge that the algorithm would vary depending on the tumour type. The LCC clinicians also stated that testing for NTRK gene fusion should be performed at the time of initial diagnosis, using previously resected samples in some cases of patients initially diagnoses with early disease. They noted that, as technology advances, it may be feasible for testing to occur non-invasively, for example, using blood liquid biopsy. In regard to lung cancer, testing would most likely be limited to non-squamous, EGFR and ALK negative cases. The LCC clinicians identified Drilon and Shaw as opinion leaders who recommend that all NSCLC patients should be tested for NTRK translocations. The LCC clinicians anticipate that as Next Generation Sequencing becomes less expensive and more available, the issue of who to test may become less burdensome. LCC posits that routine testing across a wide range of histologies using Next Generation Sequencing is a belief shared by molecular pathologists and medical oncologists across Canada. Currently, as stated in the LCC joint clinician input, many patients pay for their tumours to be tested independently outside of health care provider jurisdiction.

The CCC clinicians stated that testing should be available at all centres, although the testing can be centralized. The POGO and CCO clinicians stated that, while access to Next Generation Sequencing should be made available to all patients, it does not necessarily need to be implemented in all cancer centres.

The single clinician input limited their statements to discuss advanced thyroid cancer and lung cancer. The clinician identified limited or no systemic therapy options for RAIR, making larotrectinib a promising drug for these patients. In regards to eligible lung cancer patients, larotrectinib was also stated to be a promising drug as patients are often refractory to radiation or other systemic therapies. In addition, larotrectinib was stated to have a low toxicity profile.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of larotrectinib for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a neurotrophic tyrosine receptor kinase (NTRK) gene fusion who meet the following additional criteria:

- Age ≥ 1 month
- Eastern Cooperative Oncology Group (ECOG) performance score of ≤3
- Tumour harbouring NTRK1, NTRK2 or NTRK3 gene fusion confirmed by a validated diagnostic testing method
- Patients eligible for larotrectinib should have no satisfactory alternative treatments or have progressed following treatment.

Other literature relevant to the pCODR review and to the Provincial Advisory Group was identified while developing the review protocol and is outlined in section 7 and 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 6.1. Outcomes considered most relevant to patients, based on input from patient advocacy groups, are indicated in bold.

Table 6.1: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators	Outcomes
• Randomized and non-randomized controlled trials • Single arm trials • Master protocol trials (basket, umbrella, or platform trials)	Adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a NTRK gene fusion. • Age ≥ 1 month • ECOG PS ≤3 • documented NTRK1, NTRK2 or NTRK3 gene fusion confirmed • no satisfactory alternative treatments or have progressed following treatment Subgroups: • Histological tumour type • Age group (pediatrics vs adults) • Type of NTRK gene fusion (NTRK1 vs NTRK2 vs NTRK3) • Performance status	Larotrectinib	In the absence of potentially comparable treatment options that specifically target NTRK gene fusions, standard of care for each histologic tumour type will be considered, e.g.: • Surgery for tumour removal • Chemotherapy • Immunotherapy • radiation therapy • Palliative care/best supportive care (BSC) when no effective treatment is available	Efficacy • ORR • Time to response • PFS • **OS** • Duration of response • Clinical benefit **Patient-reported outcomes/HRQoL** **Safety** • AEs • SAEs • WDAEs

AE = adverse event; **BSA =** body surface area; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status Scale ; **HRQoL** = health-related quality of life; **mg/m^2** = milligram per square meter of body surface; **NTRK =** Neurotrophic Tyrosine Receptor Kinase; **ORR** = - objective response rate; **OS** = Overall survival; **PFS** = progression-free survival; **SAE** = serious adverse events; **WDAE** = withdrawals due to adverse events.

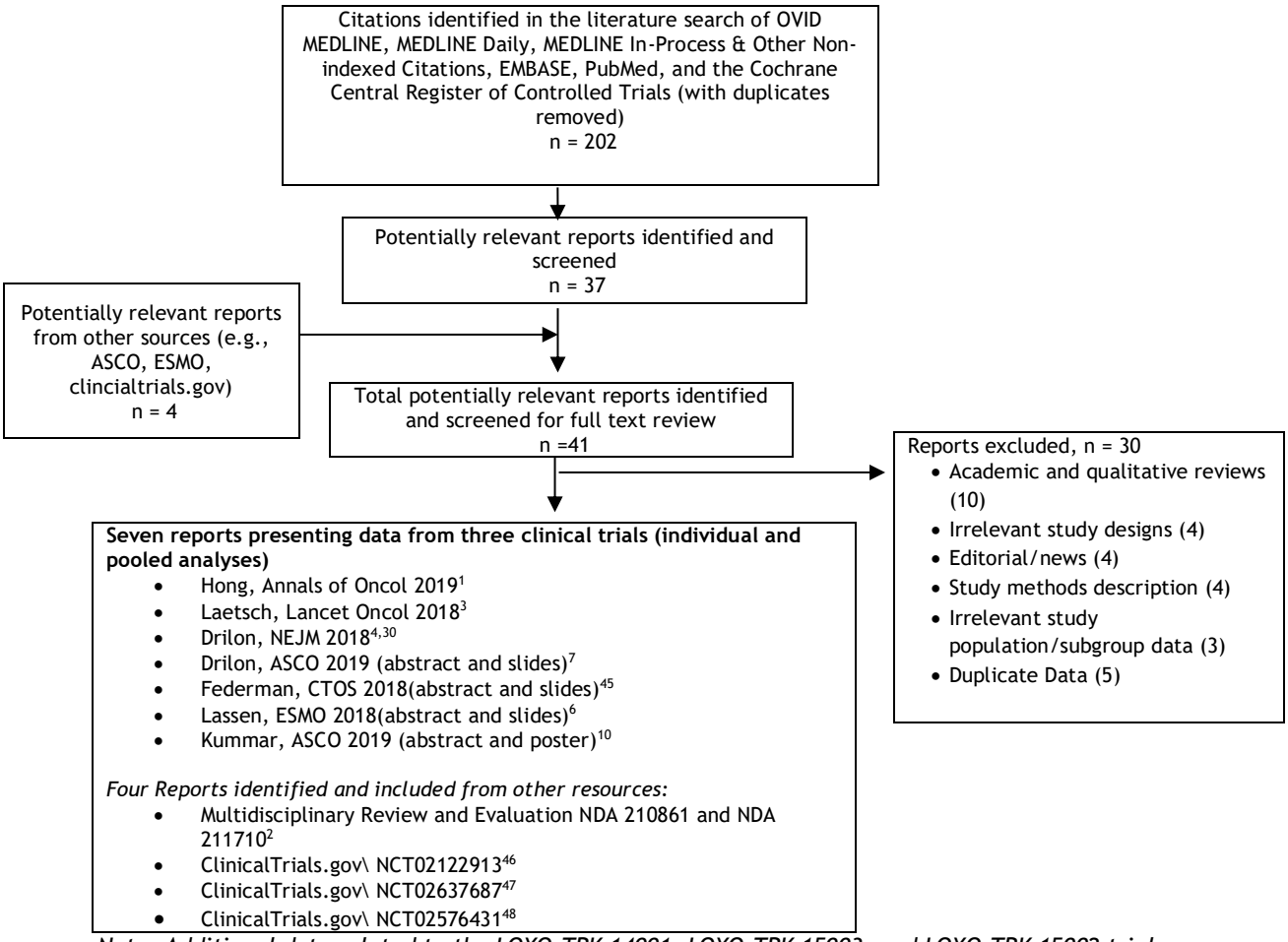
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 41 potentially relevant citations identified, 11 citations reporting data from three clinical trials were included in the pCODR systematic review,[1-3,6,7,10,30,45-48] and 30 citations were excluded. Studies were excluded because they were irrelevant study types or reviews,[31,49-61] included irrelevant patient population or subgroup data,[62-64] or if they only included a description of the study methodology.[65-68] Articles and conference abstracts reporting duplicate data from the included studies were also excluded.[69-73] Figure 6.1 illustrates the PRISMA flow Diagram for the study selection process.

Figure 6.1: PRISMA Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the LOXO-TRK 14001, LOXO-TRK 15003, and LOXO-TRK 15002 trials were also obtained through requests to the Submitter by pCODR.[5]

6.3.2 Summary of Included Studies

This pCODR review included three open-label, single-arm trials of larotrectinib in adult and pediatric patients with advanced or metastatic solid tumors (the LOXO-TRK 14001, LOXO-TRK 15003, and LOXO-TRK 15002 trials). All three trials are ongoing; however, the reimbursement submission for larotrectinib is supported with pooled analyses of efficacy and safety data from NTRK fusion cancer patients enrolled in these three trials. The submitter made the decision to pool efficacy data from patients with a NTRK fusion cancer across all three studies was made early in the development program based on global regulatory advice, after consideration of methodological challenges attributable to the rarity of NTRK positive solid tumors and multiplicity of tumor types in which NTRK gene fusions can occur.[2,5] The submitter also pointed out the following factors that permitted pooling data: the common eligibility criteria and study procedures as well as the consistency of treatment response, safety and tolerability across tumours and age groups.[5]

Characteristics of the individual trials, along with relevant information on the design and execution of pooled analyses, are summarized in section 6.3.2.1. Section 6.3.2.2 focuses on the results of the pooled analyses across the three trials. Individual study results are not presented due to small sample sizes and insufficient reporting.

6.3.2.1 Detailed Trial Characteristics

Table 6.2: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study: LOXO-TRK-14001[1,6,30] NCT02122913[46] **Characteristics**: multicentre, open-label, Phase I dose escalation study **N [total]**= 72[5,11] **N [NTRK+]** = 8 (primary analysis); 10 (integrated analysis) Number of centres and number of countries: 8 centres in US **Patient enrolment dates:**[1] 01-May-2014 – 24-August-2017 **Data cut-off:** 17-July-2017 (primary analysis) 19-February-2018 (extended analysis) 30-July-2018 (integrated analysis) **Primary completion date:** 24-August-2017 **Estimated study completion date:** 31-Dec-2019[46] **Funding**: Loxo Oncology Inc	Key Inclusion Criteria: • Adult patients (age≥ 18 years) with advanced or metastatic solid tumors • Progressed on or nonresponsive to available therapies, unfit for standard chemotherapy; or tumours with no standard or available curative therapy • ECOG PS ≤ 2 • Life expectancy ≥ 3 months Key Exclusion Criteria: • Unstable primary CNS tumors or metastasis • Clinically significant active cardiovascular disease or history of myocardial infarction • Active uncontrolled systemic bacterial, viral, or fungal infection • Current treatment with a strong CYP3A4 inhibitor or inducer • Pregnancy or lactation	Larotrectinib (oral) Dose escalation phase: 50 – 400 mg/day (50 -200 mg QD or BID) Expansion phase: 100 mg BID	Primary: • Safety • MTD Secondary: • ORR (CR + PR) • Duration of response
Study: LOXO-TRK-15003 (SCOUT trial)[3,6,30] NCT02637687[47] **Characteristics:** multicenter, open-label, Phase I/II trial **N [total]** =37[5,11]	Key Inclusion Criteria: • pediatric patients ages one month to 21 years with advanced solid or primary CNS tumours • ≥ 1 evaluable or measurable lesion (by RECIST 1.1) • Karnofsky (for patients aged ≥ 16 years) or Lansky (for patients	Larotrectinib (oral) Cohort 1: dosing according to age and bodyweight based on adult equivalent of 100 mg BID	**Phase I** Primary: • Safety • DLT Secondary: • Best overall response

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
N [NTRK+] = 12 (primary analysis); 37 (integrated analysis) **Number of centres and number of countries**: 20 centres internationally including Canada, US, EU and Australia **Patient Enrolment Dates**:[74] 16-December-2015 – ongoing **Data cut-off**: 17-July-2017 (primary analysis) 19-February-2018 (extended analysis) 30-July-2018 (integrated analysis) **Estimated study completion date**: 01-January 2022 [estimated last patient's first visit][75] **Funding**: Loxo Oncology Inc	aged <16 years) performance score of at least 50 • Patients with primary CNS tumours or brain metastases had to be stable in the past 7 days and must have not required increasing doses of steroids to manage CNS symptoms with the 7 days before study entry <u>Key Exclusion Criteria:</u> • Major surgery within 14 days before the start of larotrectinib • Clinically significant cardiovascular disease or corrected QT interval longer than 480 ms • Active uncontrolled systemic infection	<u>Cohort 2</u>: dosing according to age and bodyweight based on adult equivalent of 150 mg BID <u>Cohort 3</u>: 100 mg/m^2 BID (maximum of 100 mg twice daily)	• Duration of response • QoL **Phase II** <u>Primary:</u> • ORR (CR + PR) • DLT <u>Secondary:</u> • Duration of response • Safety
Study: LOXO-TRK-15002 (NAVIGATE trial)[6,30] NCT02576431[48] **Characteristics**: open-label, Phase II basket trial **N [total]** =75[5,11] **N [NTRK+]** = 35 (primary analysis); 75 (integrated analysis) **Number of centres and number of countries**: 21 sites in US, EU, and Asia **Patient Enrolment Dates**:[5] 13-Ocrober-2015 - ongoing[74] **Data cut-off**: 17-July-2017 (primary analysis) 19-February-2018 (extended analysis) 30-July-2018 (integrated analysis) **Estimated primary completion date**: 04-January-2023 [estimated last patient's first visit][75] **Funding**: Loxo Oncology Inc	<u>Key Inclusion Criteria:</u> • Patients age 12 and older with locally advanced or metastatic harbouring a NTRK1, NTRK2, NTRK 3 gene fusion identified through molecular assays (routinely performed at CLIA- or similarly-certified laboratories) • Received prior standard therapy appropriate for their tumour type or stage of disease, or unlikely to tolerate or derive benefit from standard of care (at the discretion of the Investigator); patients with CNS tumours must have received prior treatment including radiation and/or chemotherapy. • ≥ 1 measurable lesion (by RECIST 1.1 for patients with non-CNS solid tumours, and by RANO for patients with primary CNS tumours) • ECOG PS ≤ 3, or Karnofsky performance score of at least 50 for patients with CNS tumours <u>Key Exclusion Criteria:</u> • Symptomatic or unstable brain metastases • Unstable cardiovascular disease • inability to discontinue treatment with a strong CYP3A4 inhibitor or inducer prior to the initiation of treatment with larotrectinib •	Larotrectinib (oral) 100 mg BID	<u>Primary:</u> • ORR (CR + PR) <u>Secondary:</u> • Best overall response • Duration of response • CBR • PFS • OS <u>Exploratory:</u> • QoL • Safety

BID = twice daily**; BSA =** body surface area; **CBR** = clinical benefit rate; **CLIA** = Clinical Laboratory Improvement Amendments; **CNS** = central nervous system; **CR** = complete response; **DLT** = dose limiting toxicity; **ECOG PS** = Eastern Cooperative Oncology Group Performance Status Scale; **EU** = European Union; **mg/m^2** = milligram per square meter of body surface; **ms** = millisecond; **MTD** = maximum tolerated dose; **NTRK =** Neurotrophic Tyrosine Receptor Kinase; **ORR** = -objective response rate; **OS** = Overall survival; **PFS** = progression-free survival; **PR** = partial response; **QD** = once daily**; QoL** = quality of life; **RANO** = Response Assessment in Neuro-Oncology criteria ; **RECIST** = Response Evaluation Criteria In Solid Tumours; **US** = United States of America

a) Trials

Three clinical trials reported on the efficacy and safety of larotrectinib in adult and pediatric patients: a phase I adult dose escalation and expansion trial (study LOXO-TRK-14001, a phase I/II pediatric trial (study LOXO-TRK-15003; SCOUT trial), and a phase II basket trial in adults and adolescents (study LOXO-TRK-15002; NAVIGATE trial).

Characteristics of the included trials are summarized in Table 6.2. Additional details on the methodology of individual studies are provided below:

LOXO-TRK-14001

Study design: LOXO-TRK-14001 is a multicentre, open-label, ongoing (initiated in May 2014) phase I dose escalation and expansion trial in adult patients with an advanced or metastatic solid tumour. The trial was conducted at eight centres in the United States (US).The first part of the trial employed a 3+3 dose escalation design to enroll adults with metastatic solid tumours (regardless of NTRK gene fusion status) to six cohorts.[1] The expansion part, which is ongoing, includes two expansion cohorts: one in patients with an alteration in the NTRK1, NTRK2, or NTRK3 genes (rearrangement, fusion, or mutation), and one in patients without known NTRK alterations.[1,2,4]

Population: The study LOXO-TRK 14001 included adult patients (≥ 18 years of age), with ECOG performance score of 0-2, and locally advanced or metastatic solid tumor that had progressed, was nonresponsive to available therapies, was unfit for standard chemotherapy, or for which no standard or available curative therapy existed. Although NTRK gene fusion status was not among inclusion criteria for the trial, for the integrated analysis informing the main clinical evidence in the CADTH review, only patients with the NTRK positive gene fusion were prospectively selected for inclusion. For the NTRK cohort, evidence of an NTRK gene fusion was assessed before enrollment by next generation sequencing in a local laboratory that was certified by the clinical laboratory improvement amendments (CLIA). Patients were excluded if they had symptomatic brain metastases (for patients without central nervous system [CNS] disease) or active spinal cord compression, clinically significant active cardiovascular disease or history of prolonged QT interval; or if they were on treatment with a strong cytochrome P450 (CYP) 3A4 inhibitor or inducer.[1,2]

Intervention: In the dose escalation phase, increasing dose levels (i.e., 50 mg daily, 100 mg daily, 100 mg twice daily, 200 mg daily, 150 mg twice daily, 200 mg twice daily) were used according to the occurrence of dose-limiting toxicity (DLT) in cycle 1, or until the maximum tolerated dose (MTD) was reached. The starting dose of 50 mg once daily was determined based on data from animal toxicity studies. Patients in the expansion cohorts were treated at the MTD, or at a dose level deemed by the sponsor to provide significant TRK inhibition. Larotrectinib was administered orally once or twice daily, based on 28-day cycles. Treatment was continued until progression, unacceptable toxicity, or patient withdrawal. Dose interruptions were allowed of up to 4 weeks for clinically significant adverse events. After recovery, patients could either continue at the assigned dose of larotrectinib or receive a reduced dose. Patients with drug toxicities requiring more than 4 weeks to recover were to be withdrawn from the trial, unless there was compelling evidence of response and no alternative treatment.[1,2]

Study endpoints and outcome assessment: The primary endpoint of the study LOXO-TRK 14001 was the safety of larotrectinib (including dose-limiting toxicity) and identification of the MTD. Secondary endpoints included overall response rate (ORR) and duration of response (DOR). Best overall response was determined based on the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) for primary solid tumors and by the Response Assessment in Neuro-Oncology (RANO) criteria for primary CNS tumours. Duration of DOR was defined as the number of months from the start date of complete or partial responses

(whichever was observed first) to the first date that recurrent or progressive disease was objectively documented. Tumor assessments were conducted on or prior to Day 1 of Cycles 3, 5, 7, 9, 11, and 13, and every 3 cycles thereafter until the onset of progressive disease. The severity of each adverse event (AE) was graded by the investigators using the National cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE; version 4.03), when applicable[1,2]

Statistical analysis plan: The dose escalation portion of the study employed a classical "3+3" dose escalation design, with 3 to 6 patients enrolled in each cohort.[1] A sample size of approximately 60 patients was required to define the MTD of larotrectinib. Assuming the true ORR to be 50%, a total of 40 patients (20 patients in each expansion cohort) were required to provide 91% power to exclude 30% from the lower bound of the 90% confidence interval for ORR.[2] Safety results were summarized descriptively. The estimates of ORR were confirmed by one- and two-sided confidence intervals (CIs) with various coverage probabilities (e.g., 80%, 95%).[2,4]

LOXO-TRK-15003 (SCOUT trial)

Study design: The SCOUT trial is a multicentre, open-label, phase I/II trial in pediatric patients with advanced solid or primary CNS tumours. The study was conducted at 20 sites, internationally, and consisted of two parts:

The Phase I dose escalation part of the trial used a modified rolling six dose escalation design, with the purpose of identifying the MTD and evaluating pharmacokinetics of larotrectinib. Between 3 and 9 patients were enrolled into each of five planned dose levels, or until the MTD was reached. Enrolment to cleared cohorts remained open, without an enrolment cap, to eligible patients with NTRK gene fusions during toxicity assessments and protocol amendments.[3] The recommended phase II dose (RP2D) of larotrectinib in pediatric patients (100mg/m^2 twice daily, up to 100mg twice daily) was declared on 13-April-2017, and used to obtain additional safety data in an expansion cohort of up to 18 patients.[2] In phase II, eligible pediatrics patients with tumours harbouring a NTRK gene rearrangement or non-resistant mutation were enrolled into the following three cohorts: infantile fibrosarcoma (IFS), other extracranial solid tumors, and primary CNS tumors. The objectives of phase II were to evaluate anti-tumour activity of larotrectinib in each of the aforementioned tumour types and to further evaluate safety profile of larotrectinib at the recommended dose for pediatrics.[2]

Population: The SCOUT trial included infants, children, and adolescents aged 1 month to 21 years with locally advanced or metastatic solid tumours or CNS tumours that had relapsed, progressed, or had inadequate response to available therapies. To be eligible patients were required to have a Karnofsky (if ≥16 years of age) or Lansky (if <16 years of age) performance status score of 50 or more, evaluable or measurable disease according to RECIST, adequate organ function, and full recovery from the acute toxic effects of all previous anticancer therapy. The protocol amendment issued on 12-September-2016 expanded the inclusion criteria to include patients with locally advanced IFS who would require disfiguring surgery to achieve a complete surgical resection. NTRK gene fusion status was not part of the eligibility criteria of the SCOUT trial (except for infants aged one month to less than one year). However, evidence of an NTRK gene fusion was assessed in a local laboratory.[3]

Intervention: In phase I dose escalation, patients received larotrectinib orally according to SimCyp® dose escalation modeling for Cohorts 1 and 2 (that took both age and body surface area [BSA] into consideration), and with a BSA-based dose for Cohort 3 and subsequent cohorts. In phase expansion and phase II, the starting dose of100 mg twice

daily was used based in previous testing in adults. Larotrectinib was administered orally twice daily, based on 28-day cycles. Treatment was continued until progression, unacceptable toxicity, or patient withdrawal[2-4] Treatment might enter a "wait and see" drug discontinuation period following the time of best response after a minimum of 6 cycles of treatment. Re-treatment with larotrectinib could be an option if patients showed evidence of disease progression after drug discontinuation. Patients who undergo surgical resection for local control may continue to receive larotrectinib after surgical recovery (at the discretion of the Investigator).[2,4]

Study endpoints and outcome assessment: The primary endpoint of the phase I dose escalation component was the safety of larotrectinib, including dose-limiting toxicity. Secondary outcomes of phase I included the MTD or the appropriate dose of larotrectinib for further clinical investigation, the pharmacokinetics of larotrectinib. The anti-tumour activity of larotrectinib was assessed in phase I expansion and phase II through measurement of ORR (per RECIST version 1.1), PFS, OS, and assessment of pain and health-related quality of life (HRQOL).[3] All treated patients underwent a safety follow-up visit at 28 days ($\pm$ 7 days) after the last dose and long-term follow up visits at 3-month intervals ($\pm$ 1 month) and until the study is officially closed.[4]

Statistical analysis plan: A total of 36 patients were planned for the dose escalation phase in order to define the MTD of larotrectinib. The Phase 1 expansion cohort enrolled approximately 18 additional patients. Assuming the true ORR to be 50%, a total of 30 patients (10 patients per cohort) were planned for the second part of the study in order to exclude an ORR of 27% from the lower bound of the 95% confidence interval for the observed ORR.[2] The safety population included all patients who received one or more doses of larotrectinib. Anti-tumour activity was assessed in all enrolled patients The estimates of ORR were accompanied by two-sided exact binomial 95% CI, using the Clopper- Pearson method.[2,4]

Results of the phase I dose-escalation part of the trial were published in Lancet Oncology in 2018;[3] the phase I long term follow up and phase II parts are ongoing and the results are yet to be published.[3]

LOXO-TRK-15002 (NAVIGATE trial)

Study design: The NAVIGATE trial is an ongoing open-label, phase II, multicentre trial in adolescent and adult patients with advanced cancer harboring a fusion of NTRK1, NTRK2, or NTRK3. The trial consisted of nine cohorts of patients with solid tumors bearing NTRK fusions, including: 1) non-small cell lung cancer, 2) thyroid cancer, 3) sarcoma, 4) colorectal cancer, 5) salivary gland cancer,6) biliary cancer, 7) primary CNS tumor, 8) all other solid tumor types with evaluable but not measurable disease; and 9) patients with an NTRK gene fusion identified in a lab where certification of the lab cannot be confirmed by the Sponsor.[4] The study consisted of a screening period, a treatment period, a safety follow up visit, and long-term follow up assessments. Safety, survival, and subsequent anticancer therapies would be tracked during the long-term follow-up period.[4]

Population: The NAVIGATE trial included patients 12 years of age and older with ECOG performance score of 0-3. To be eligible, patients were required to have a locally-advanced or metastatic cancer with an NTRK1, NTRK2 or NTRK3 gene fusion, identified through molecular assays as routinely performed at CLIA or other similarly certified laboratories; have received prior standard therapy (any line of treatment) or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy. Patients in Cohorts 1-6 must have at least one measurable lesion (per RECIST version 1.1). Patients in cohort 7 (primary CNS

tumors) must have received prior treatment including radiation and/or chemotherapy, have ≥1 site of bi-dimensionally measurable disease (per RANO criteria), and have imaging study performed within 28 days before enrollment. Patients with solid tumors without RECIST measurable disease (e.g., evaluable disease only) were eligible for enrollment to Cohort 8, regardless of tumor type. Patients were excluded if they had symptomatic or unstable brain metastases (patients with asymptomatic brain metastases and patients with primary CNS tumors were eligible), unstable cardiovascular disease, and inability to discontinue treatment with a strong CYP3A4 inhibitor or inducer prior to treatment initiation.[4]

Intervention: Larotrectinib was administered 100 mg orally twice daily, based on 28-day cycles. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal. Patients who developed investigator-assessed disease progression (per RECIST 1.1) might be allowed to continue larotrectinib.[4] For patients who experienced a clinically significant hematologic or non-hematologic treatment-emergent AE (greater than Grade 2, or more than one grade increase from baseline if baseline was Grade 2 or higher) larotrectinib dosing was held for up to four weeks to evaluate the AE and to allow for recovery (to Grade 1 or baseline level). In patients who had previously benefited from larotrectinib per-investigator assessment, larotrectinib dosing could be held for more than four weeks to allow resolution of AEs, with the sponsor's permission.[2]

Study endpoints and outcome assessment: The primary endpoint of the NAVIGATE trial was ORR, defined as the best overall response of confirmed CR or PR as determined by an independent radiology review committee (IRC) using RECIST (version 1.1) or RANO criteria, as appropriate to tumor type. Secondary endpoints included: investigator-assessed ORR, DOR: CBR, PFS, OS and safety. Patients underwent radiographic evaluation of their disease at the end of even-numbered cycles between Cycles 1-12, and every three cycles thereafter. Patients with primary CNS disease underwent radiographic evaluation of their disease at the end of each cycle between Cycle 1 and Cycle 4, and every 2 cycles between Cycle 5 and Cycle 12, and every three cycles thereafter.[2,4]

Patient-reported outcomes were measured using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and European Quality of Life 5-Five Dimensions 5-Levels Health Questionnaire (EQ-5D-5L) for patients age 18 years and older, and the Pediatric Quality of Life-Core Module (PedsQL) for patients age 12 to 17.[2,76]

Statistical analysis plan: Up to 18 patients per tumor-specific cohort (Cohorts 1-7), and up to 25 patients in the other histologic tumour types cohort (Cohort 8) or patients without measurable disease cohort (Cohort 9), were estimated; with an expected total sample size of approximately 151 patients at up to 40 sites. Patients who did not have any radiological disease assessments after the initiation of larotrectinib would be replaced.[4]

For the Cohorts 1 through 7, Simon's 2-stage design was used to assess anticancer activity of larotrectinib in each tumour type. For each cohort, a true ORR of 10% or less is considered insufficient to warrant further study (null hypothesis), whereas a true ORR of 30% or more is considered sufficiently effective (alternative hypothesis). The number of patients evaluated in each stage and the minimum number of responders needed to continue to the next stage were determined based on the optimum version of the aforementioned design with 80% power and one-sided significance level of 10%. Based on the above design considerations, up to 7 patients might be enrolled in each cohort (stage 1). If no patients achieved CR or PR (confirmed or unconfirmed) within a cohort, then enrollment within that cohort would terminate. Otherwise, 11 additional patients would be enrolled within the cohort (second stage). Up to 18 patients per tumor-specific cohort (Cohorts 1-7), and up to 25 patients in the other histologic tumour types cohort (Cohort 8)

or patients without measurable disease cohort (Cohort 9), were estimated; with an expected total sample size of approximately 151 patients at up to 40 sites. In case seven patients with the same histology were enrolled without a response, then no further patients would be enrolled with that histology.[4]

Analysis of the primary efficacy endpoint was based on the Full Analysis Set which included all patients who received at least one dose of larotrectinib and had undergone at least one radiological disease assessment after initiation of larotrectinib. Patients who did not have any post-baseline radiological disease assessments (irrespective of reason including death) would be replaced. Exploratory subgroup analyses of selected efficacy endpoints were planned to be performed, subject to the availability of data. The subgroups would be defined based on the patient and disease characteristics as well as treatment history (e.g., extent of prior therapy). The point estimate of the ORR was calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best overall response of CR or PR), and its one-sided 90% CI was estimated using an exact inference method that appropriately accounted for the 2-stage design feature.[4]

DOR was calculated for patients who achieved CR or PR. Time-to-event endpoints (i.e., DOR, PFS, and OS) were summarized descriptively using the Kaplan-Meier method with 95% CIs calculated using Greenwood's formula.[4]

b) Pooled Analyses:

The pooled analyses included data from patients with NTRK gene fusions enrolled in each of these three clinical trials (Figure 6.2).

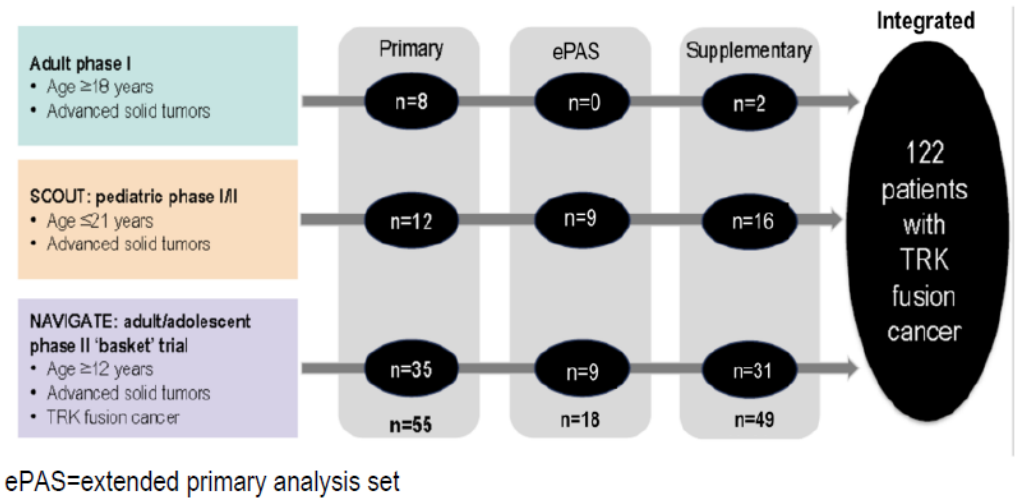
Data sets: The following data sets were used for the pooled analyses:[5]

1) Primary dataset (17-July-2017 data cut-off) included the first 55 patients across the three studies (8 patients form LOXO-TRK-14001, 12 patients from SCOUT, and 35 patients from NAVIGATE) who met the inclusion criteria for the pooled analysis. This dataset comprised the FDA submission and was initially published on February 22, 2018 as a peer-reviewed article in the New England Journal of Medicine.[30]
2) Extended Primary dataset (19-February-2018 data cut-off) included an additional 18 patients (9 patients from SCOUT, and 9 patients from NAVIGATE) who met inclusion criteria for the pooled analysis. A total of 73 patients with NTRK gene fusions were analysed at this data cut-off date. The results of the extended primary analysis were submitted to Health Canada for regulatory review.
3) Supplementary dataset (30-July-2018 data cut-off): included an additional 49 patients across the three studies (2 patients form LOXO-TRK-14001, 16 patients from SCOUT, and 31 patients from NAVIGATE).
4) Integrated dataset (30-July-2018 data cut-off) consists of 122 patients from the Extended primary and Supplementary datasets, combined; i.e., larotrectinib-treated patients with NTRK gene fusions, who had their outcomes assessed by the investigator.
5) Safety dataset (30-July-2018 data cut-off) encompasses the entire larotrectinib safety database (n=207), which includes 122 patients with NTRK gene fusion cancer and 70 patients without confirmed NTRK gene fusions.

Pooled analysis plan: The efficacy analyses were performed according to the intention-to-treat (ITT) principle. With the aim to obtain a true overall response rate of at least 50%, a sample size of 55 patients, used for the primary pooled analysis, would provide 80% power to rule out a lower limit of 30% for the overall response rate at a two-sided significance level of 0.05.

The primary endpoint for the analysis of efficacy was overall response rate (ORR) determined by IRC. ORR was defined as the proportion of patients with best overall response (i.e., confirmed complete response [CR] or confirmed partial response [PR] based on RECIST 1.1) recorded between the date of the first dose of larotrectinib and the date of documented disease progression or the date of subsequent therapy or cancer-related surgery, whichever occurred first.[2] Secondary endpoints included duration of response (DOR), PFS and safety.[6] DOR was defined as the number of months from the start date of PR or CR (whichever response was recorded first, and subsequently confirmed) to the date of disease progression or death, whichever occurred earlier.[2] Confidence intervals (CI) were calculated with the use of the Clopper–Pearson method. Duration of response and progression-free survival (PFS) were estimated by the Kaplan–Meier method according to the investigators' assessments of response, with the 95% CI around the median calculated using Greenwood's formula.[2]

Figure 6.2: Pooled analysis of efficacy data from three larotrectinib trials



Data cut-off date: 30- July-2018

Source: [02.00.01_Vitrakvi_Note to Clinical Reviewer; Figure 13, page 21][5]

Pooled analysis population: Adults and pediatrics enrolled across the three larotrectinib studies were included in the pooled efficacy analysis if they met the following criteria:

- documented NTRK gene fusion as determined by local testing;
- non–central nervous system primary tumour with one or more measurable lesions at baseline that could be assessed according to RECIST, version 1.1; and
- received one or more doses of larotrectinib.

The safety analysis included all 122 patients with NTRK gene fusion cancer (efficacy analysis population) plus 70 patients who were included in any of the three larotrectinib studies without a confirmed NTRK gene fusion.[2,5] Patient ages ranged from 1.2 months to 80 years, with a median of 41 years. The majority of patients had a ECOG performance score of 0 or 1; and 45% of patients had received two or more prior systemic anti-cancer therapies (Table 6.3).[5,6]

Table 6.3: Baseline characteristics of the patients included in the pooled analysis of efficacy from larotrectinib trials (LOXO-TRK 14001, 15003, and 15002)

Characteristic	Primary Analysis (n=55)	Extended Primary Analysis (n=73)	Integrated Analysis (n=122)
Gender, n (%)			
Male	29 (53)	38 (52)	60 (49)
Female	26 (47)	35 (48)	62 (51)
Median age (range), years	45.0 (0.3-76.0)	41.0 (0.1-76.0)	41.0 (0.1 – 80.0)
ECOG PS, n (%)			
0	24 (44)	33 (45)	59 (47)
1	27 (49)	33 (45)	53 (43)
2	4 (7)	7 (10)	12 (10)
No. of prior systemic regimens, n (%)			
0-1	27 (49)	15 (21)	66 (54)
2	9 (16)	35 (48)	25 (20)
≥3	19 (35)	23 (32)	31 (25)
Histological tumour type, n (%)			
Appendix	1 (2)	1 (1.4)	1 (0.8)
Bone sarcoma		2 (2.7)	2 (1.6)
Breast	1 (2)	1 (1.4)	2 (1.6)
Cholangiocarcinoma	2 (4)	2 (2.7)	2 (1.6)
Colon	4 (7)	6 (8.2)	6 (4.9)
Congenital Mesoblastic Nephroma		1 (1.4)	1 (0.8)
GIST	3 (5)	5 (6.8)	5 (4.1)
IFS	7 (13)	10 (13.7)	18 (14.8)
Lung	4 (7)	4 (5.5)	11 (9.0)
Melanoma	4 (7)	4 (5.5)	7 (5.7)
Pancreas	1 (2)	1 (1.4)	1 (0.8)
Salivary gland	12 (22)	13 (17.8)	19 (15.6)
STS (other)	11 (20)	17 (23.3)	28 (22.9)
Thyroid	5 (9)	6 (8.2)	18 (14.8)
Unknown primary			1 (0.8)

Data cut-off date: 30-July-2018

Source: [02.00.01_Vitrakvi_Note to Clinical Reviewer; Table 4, page 21-22][5]

Pooled analysis intervention: The pooled analysis included patients with NTRK gene fusions who were enrolled in one of the three larotrectinib trials and were treated with larotrectinib 100 mg orally twice daily in individuals with body surface area (BSA) ≥1 m^2, or 100 mg/m^2 orally twice daily for children with a BSA <1 m^2.[5,30] It is not clear if patients enrolled in the dose escalation phase were included in or excluded from the pooled analysis.

c) Patient Disposition

A total of eligible 122 patients with NTRK gene fusions, from the three aforementioned trials, were included in the Integrated pooled analysis (); of those, 83 patients (68%) remained on treatment at the time of data cut-off (i.e., 31-July-2018) and 39 patients (32%) discontinued treatment. Reason for discontinuation included disease progression in 28 patients (23%), adverse events in two patients (<2%), patient withdrawal in two patients (<2%), and other reasons in 7

patients (6%).[5] At the data cut-off date, a total of 15 (12%) patients continued larotrectinib post-progression, while 18 (15%) discontinued treatment post-progression.[5]

Protocol Violations/Deviations: As of 17-July-2017 data cut-off date, the major protocol deviations in the included larotrectinib trials were as follows:[2] It is not clear how many patients in the pooled analysis had protocol deviations.

- LOXO-TRK-14001: A total of 392 protocol deviations were reported, affecting 65 patients. Of these, 24 were considered to be significant, including deviations relating to the investigational product (n = 9), informed consent (n = 5), inclusion/exclusion criteria (n=4), study procedures (n=4), and restricted concomitant medication (n=2). None of the protocol deviations were considered, by the submitter, to have an impact on the safety or efficacy results.
- LOXO-TRK-15003 (SCOUT trial): A total of 152 deviations were identified, affecting 27 patients. The majority of protocol deviations were related to missed individual tests specified by the protocol and were considered to be minor. Eight deviations were considered significant, including protocol eligibility exceptions in four patients; and deviations relating to informed consent, study drug, concomitant medication, and study procedures categories (one patient each).
- LOXO-TRK-15002 (NAVIGATE trial): A total of 223 protocol deviations were reported, affecting 38 patients. Of these, 23 protocol deviations (affecting 17 patients) were considered to be significant, including deviations relating to protocol-defined assessments (n=3), non-compliance with the study drug (n=1), reporting of serious adverse events (n=2), study treatment dose (n=1), eligibility criteria (n=1), compliance with withdrawal criteria (n=1), and prohibited concomitant medication (n=4).

Based on the Center for Drug Evaluation and Research multidisciplinary review report, at the19-February-2018 data cut-off date (60-day update), one patient had been withdrawn from the study due to a protocol violation.[2]

d) Limitations/Sources of Bias

Focus on molecular profiling

NTRK gene fusions can occur in various tumour types with different natural histories. The primary objective of the included single arm trials and that of the submitted integrated analysis was not to determine the effect of the drug separately in each tumour type. The treatment effect was rather estimated irrespective of histological tumour type. In other words, an assumption was made by the investigators that the presence of a NTRK gene fusion was sufficient to evaluate the effect of larotrectinib in all relevant tumour types.

Scarcity of historical data

The Submitter acknowledged that there was no literature that demonstrated the impact of NTRK gene fusion proteins on patients' outcomes across tumour types.[5] An independent literature search that was conducted by the pCODR review team was also unable to find studies with acceptable methodological quality that investigated the effects of current standard of care in NTRK positive solid tumours (see section 7). NTRK gene fusions are rare and the natural history of the disease has not been well characterized to date.

In addition, there is a lack of data on comparative efficacy and safety for tumor types that have relevant comparators available. VOYAGER-1 is an ongoing retrospective cohort study that uses secondary data to study the patient characteristics and clinical outcomes in cancer patients with NTRK gene fusion and those in cancer patients without NTRK mutations who received current standard of care in a real-world setting (see section 6.4 for more details). However, as the study is ongoing, outcome results are not currently available.[5]

Heterogeneity in design elements of studies included in the pooled analysis

Interpretation of pooled analysis results remain difficult in the presence of between-study heterogeneity:

i. Different phased studies: Given the rare nature of NTRK fusion positive solid tumors and methodological challenges, the Submitter rationalized that the conduct of a randomized trial was not feasible.[2,5] Therefore, the submitted data was pooled from three single arm trials: a phase I adult trial (LOXO-TRK 14001), a phase I/II pediatric trial (SCOUT), and a phase II basket trial (NAVIGATE) in adults and adolescents. The phase II part of the SCOUT trial, investigating long-term safety and efficacy of larotrectinib in pediatric patients is ongoing and results are yet to be published.

ii. Different primary outcomes: The primary objective of the dose escalation phases of the LOXO-TRK 14001 and SCOUT studies was to determine the safety and tolerability of larotrectinib, while the primary objective of the NAVIGATE trial was to determine the efficacy of larotrectinib by measuring the best overall response rate. The dose expansion cohorts included in the LOXO-TRK 14001 and SCOUT phase I trials were powered to detect a 30% or larger improvements in ORR, as their secondary study objective.

iii. Different requirements for outcome measurement: In the LOXO-TRK 14001 and SCOUT trials, ORR was assessed by the investigator using RECIST (version 1.1) or RANO criteria, as appropriate to tumor type; whereas in the NAVIGATE trial, ORR was determined by an independent radiology review committee using RECIST (version 1.1) or RANO criteria.

iv. Different eligibility criteria: As mentioned earlier in this section, LOXO-TRK 14001 included adult patients, SCOUT included pediatric and NAVIGATE enrolled adults and adolescent patients. In addition, the presence of a confirmed NTRK fusion was mandated before enrollment in the NAVIGATE trial; while NTRK positive status was not a requirement for eligibility in the LOXO-TRK 14001 and SCOUT trials. TRK gene fusions were identified

prospectively in the two latter trials. These sources of heterogeneity in the patient selection criteria may introduce bias to the results of the pooled analysis.

Uncertainty around the pooled analysis results

The following limitations should be considered when interpreting the pooled analysis results:

i. Pooled estimates of response versus survival outcomes: Due to the small sample size, there is uncertainty regarding the magnitude of the treatment effect of larotrectinib in any one histologic subtype of solid tumors with an activating NTRK rearrangement. The Clinical Guidance Panel agreed that the pooled ORR estimate for treatment effect was generalizable to all of the subgroups. However, pooling data across tumour types may lead to inflated type I error if the treatment effect is heterogenous across different tumour types.[12] Subgroup analyses of data from the three larotrectinib trial (integrated analysis; n=122) indicated that ORR results varied across tumour types. The reported ORR benefit ranged from 100% in thyroid cancer, gastrointestinal stromal tumor (GIST), and cellular congenital mesoblastic nephroma (CMN) down to 0% in appendix, pancreas and breast cancers, and cholangiocarcinoma (see Table 6.6 for more details). Additionally, imbalanced and small sample sizes for each tumour type could lead to inefficient tumour subgroup analyses, due to lack of statistical power. In the above-mentioned subgroup analysis, there was one patient enrolled in each of appendix, breast CMN and pancreas tumour subgroups.

   Pooling data on survival outcomes (i.e., PFS and OS) could be even more problematic, if there is a variability in the PFS or OS across different tumour types. This is because traditional survival analysis methods such as Kaplan-Meier (KM) curves relies on the assumption that a single survival distribution can be used to estimate the survival of all study participants.

   Novel methodological approaches have been proposed to improve the design and analysis of single-arm basket trials and account for potential heterogeneity of response rates across various tumour types. Limited information was available on the use of such methodology in the current review but was deemed non-disclosable by the submitter.[12-15]

ii. Ongoing nature of the included trials: All three larotrectinib trials are ongoing. The LOXO-TRK-14001 trial has stopped enrollment in 2017; however, NAVIGATE and SCOUT are still enrolling patients. Therefore, the results of the pooled analysis are subject to change as more data becomes available.

iii. Risk of selection and immortal time biases: In the NAVIGATE trial, patients who did not have any radiological disease assessments after the initiation of larotrectinib would be replaced by new patients who had a documented disease assessment.[4] It is not clear if the same criterion was used in the LOXO-TRK 14001 and SCOUT trials. Detailed patient disposition data is not available for the pooled integrated analysis. However, Based on the CONSORT flow diagram for the Extended Primary analysis (n=73; 19-February-2018 data cut-off), of the first 105 consecutively enrolled and treated patients (across all three trials, 20 patients were excluded from efficacy analysis due to insufficient follow-up to allow Independent Review Committee assessment; six patients were excluded because they did not have a RECIST measurable disease at enrolment; and six additional patients were excluded due to primary central nervous system (CNS) tumors.[5] It is however not clear how many of these patients were replaced. Exclusion of patients with no disease assessment may have introduced bias by selecting patients who had a better compliance. In addition, patients must survive until the first disease assessment visit to have a radiological disease assessment (immortal time bias).

iv. Uncertainty around quality of life data: In addition to the uncertainty in determining the magnitude of effect using pooled data from such a heterogenous population, the number of patients with available HRQoL data is low. The Methods team therefore agree that the HRQoL results are exploratory and should be interpreted with caution.

The use of PFS ratio (PFSr) as an indicator of clinical efficacy

PFSr, also referred to in the literature as the growth modulation index,[16-18] is defined as the ratio of PFS on the last line of therapy (larotrectinib, in the case of the current pCODR review) to the PFS on the most recent prior line of therapy.

In the feedback received from the Sponsor on the initial pERC recommendation, 65% of the larotrectinib-treated patients in the extended primary analysis dataset were reported to have a PFSr equal to or greater than 1.3 (a threshold proposed by Von Hoff et al.[17] as a sign of drug activity). The Sponsor suggested that the PFSr comparison would help address pERC's concerns of heterogeneity of tumour type.[5]

The Methods team acknowledges that PFSr provides an intra-patients drug activity comparison between two consecutive lines of therapy in order to eliminate heterogeneity (between-patient variability). However, the following methodological limitations should be considered when interpreting the PFSr results reported for the pooled analysis of the larotrectinib trials:

i. The Analysis of PFSr was not specified as a clinical endpoint in the included larotrectinib study protocols but was added as an exploratory, post-hoc analysis to support the primary clinical efficacy findings.

ii. All patients included in the larotrectinib trials (and in the pooled analyses) received their prior lines of therapy before enrollment in the study. As a result, data on PFS1 was most likely collected retrospectively. No information was provided in the study reports on the data collection procedures and missing data. It is not clear if the timing and frequency of disease assessment were consistent between larotrectinib therapy and the previous line of treatment; and if data on PFS1 was available for all enrolled patients. Overall the risks of ascertainment and attrition biases could not be ruled out.

iii. The methods team was unable to identify any studies that validated PFSr with other measures of clinical benefit (e.g., overall survival) in studies of drugs targeting NTRK gene fusions. Another methodological issue inherent to PFSr is that the use of this indicator to assess clinical benefit is dependent on the correlation between PFS1 and PFS2. For example, a patient with a good response to both larotrectinib and their previous line of therapy would attain a lower PFSr.[19,20]

Factors limiting the external validity of the pooled analysis

Other potential limitations of the pooled analysis include:

i. The larotrectinib trials included patients with NTRK+ solid tumours regardless of their tumour type. However, not all solid tumor types were represented in the studies.

ii. The pooled analysis excluded patients with primary CNS tumours.

iii. The eligibility criteria for the three larotrectinib trials did not restrict the number of previous lines of systematic therapy.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Overall Response Rate (ORR)

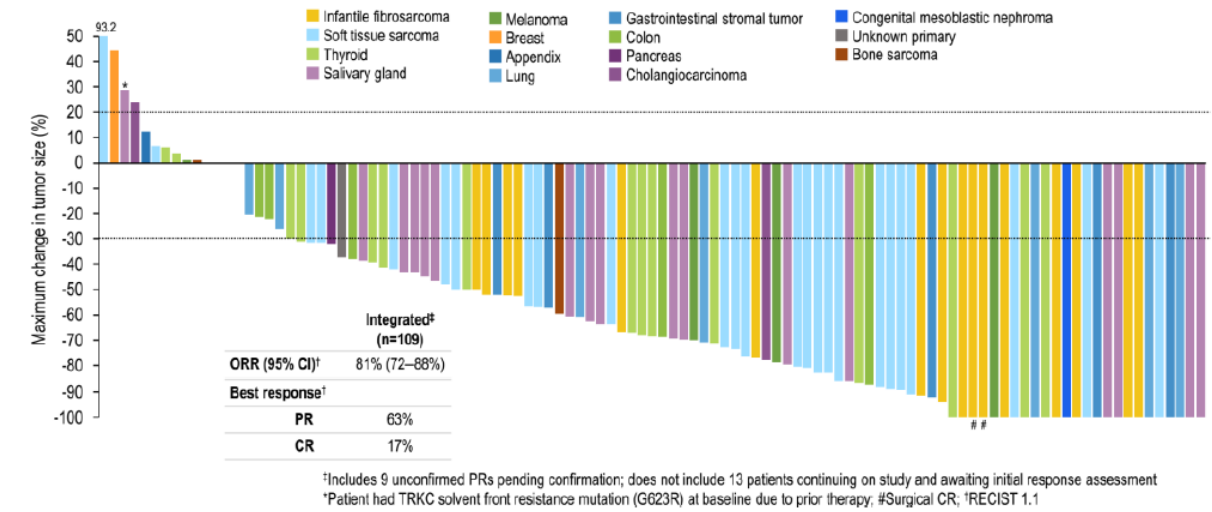
ORR was the primary endpoint of the pooled analyses:

- ORR from the Primary analysis set (N= 55; 17-July-2017 data cut-off) was 75% (95% CI 61%, 85%); 13% of patients achieved a CR and 62% achieved a PR.[30]
- In the Extended Primary database analysis (N=73; 19-February-2018 data cut-off) the ORR estimate remained consistent at 75% (95% CI 64%, 85%), with 22% of the patients had achieved a CR.[5]
- ORR from the Integrated Analysis set (N= 122; 30-July-2018 data cut-off date) was 81% (95% CI 72%, 88%); 17% of patients achieved a CR and 63% achieved a PR (Figure 6.5).[5,6]

At the 30-July-2018 data cut-off date, 84% of responding patients (73% of all patients) remained on treatment or had undergone surgery with curative intent.[5]

The median time to response was 1.8 (range 0.9 to 6.4) months in the Primary analysis, and remained consistent (i.e., 1.8 months) in the Extended Primary and Integrated analyses.[5,30]

Figure 6.3: Objective response rate in patients with NTRK gene fusions from three larotrectinib trials (Integrated analysis)



Data cut-off date: 30-July-2018

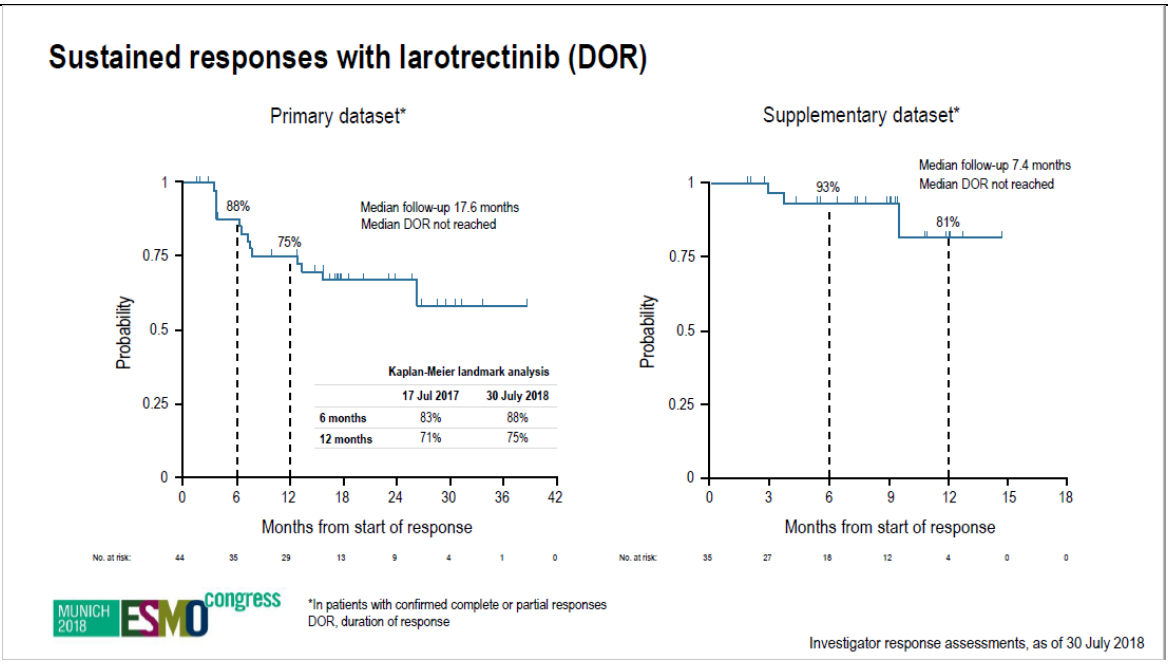
Source: [02.00.01_Vitrakvi_Note to Clinical Reviewer; Figure 14, page 22][5]

Duration of Response (DoR)

As of the 17-July-2017 data cut-off date (Primary analysis), after a 17.6 months median duration of follow up, the median duration of response (investigator-assessed) had not been not reached. The percentage of patients with an ongoing response was 83% at 6 months, and 71% at 12 months from the start of response (Figure 6.4).

As of the 30-July-2018 data cut-off date, the median duration of response had not been reached. The percentage of patients with an ongoing response was 88% at 6 months, and 75% at 12 months from the start of response.[5,6]

Figure 6.4: Duration of response in patients with NTRK gene fusions from three larotrectinib trials (Primary and integrated analyses)



Note: The supplementary dataset in this figure includes data from 67 NTRK patients, who were added to the Primary dataset of 55 patients. This number is a combination of the 18 patients form the extended analysis (added by the 19-February-2018 data cut-off) and 49 patients from the supplementary data set (added by the 30-July-2018 data cut-off date; see Figure 6.2 for more details)

Source: [Lassen ESMO 2018 presentation (provided by the Submitter)][6]

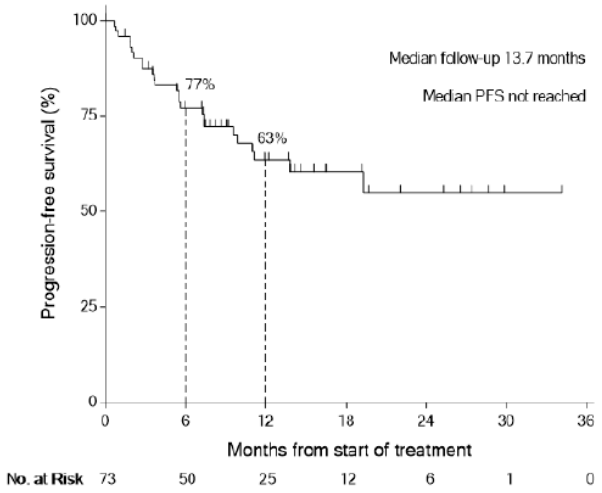
Progression-Free Survival (PFS)

As of the 17-July-2017 data cut-off date (Primary analysis), after a median follow-up of 9.9 months, the median PFS had not been reached, and 55% of patients had no progression at 12 months. At the 19-February-2018 data cut-off, after a median follow-up of 15.6 months, the median PFS for the Primary analysis had not been reached. Consistent results were reported from the analysis Extended Primary dataset, indicating that after a median follow-up of 13.7 months, the median PFS had still not been reached (Figure 6.5)

At the 30-July-2018 data cut-off date (Integrated analysis), after a 19.6 months median duration of follow-up for the Primary dataset, the median PFS was 28.3 months (95% CI 9.9, not estimable). In their report, the Submitter acknowledged that this estimate was "not statistically stable due to a low number of progression events, as evidenced by the wide confidence interval".[5] Kaplan-Meier curves for PFS are not available from the Integrated analysis.

In the feedback received from the Sponsor on the initial pERC recommendation, progression-free survival ratio (PFSr), defined as the ratio at the PFS under line +2 (PFS2) divided by the PFS at line +1 (PFS1)[5], was considered as a "direct intra-patient evaluation of treatment benefit". Based on the Sponsor's feedback, a PFS2/PFS1 ratio >1.3 would be indicative of a clinically meaningful treatment effect.[8] It was reported in the feedback document that, although PFS was ongoing for many patients treated with larotrectinib in the extended primary analysis set (n=73), 65% of these patients had attained a PFSr ≥ 1.3.[9]

Figure 6.5: Progression-free survival in patients with NTRK gene fusions from three larotrectinib trials (Extended Primary analysis)



Data cut-off date: 19-February-2018

Source: [02.00.01_Vitrakvi_Note to Clinical Reviewer; Figure 17, page 25][5]

Overall Survival (OS)

The submitted pooled OS analysis was based on the Extended Primary dataset (n= 73; median follow up 14.8 months). OS results are not available from the Primary and Integrated analyses.

As of the 19-February-2018 data cut-off, 63/73 patients (86.3%) were alive and 10/73 patients (13.7%) had died in the Extended Primary dataset. The median OS had not been reached. At 12 months, the probability of survival was estimated to be 90% (Figure 6.6).[5].

Figure 6.6: Overall survival in patients with NTRK gene fusions from three larotrectinib trials (Extended Primary analysis)

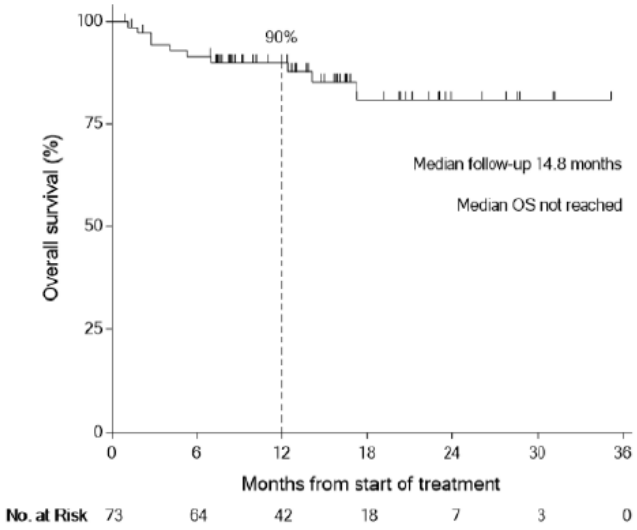


Figure 6.6: Overall survival in patients with NTRK gene fusions from three larotrectinib trials (Extended Primary analysis)

Data cut-off date: 19-February-2018

Source: [02.00.01_Vitrakvi_Note to Clinical Reviewer; Figure 18, page 25][5]

Subgroup Analyses of the primary efficacy endpoint

Subgroup analyses were performed to compare the ORR by age, tumour type, baseline disease characteristics, and NTRK gene fusions.

ORR was consistent across all subgroups based on baseline disease characteristics (ECOG status and metastatic cancer status), and number of prior treatment regimens (Table 6.4). Response rates were numerically higher with better baseline ECOG status, locally advanced tumours (versus metastatic tumours), and with fewer prior regimens. However, the observed ORR differences should be interpreted with caution, due to the overlapping confidence intervals.

The subgroup analyses of ORR indicated that ORR results varied across patient age groups (Table 6.5), tumour types (Table 6.6), and NTRK gene fusion or major NTRK isoforms (Table 6.7).[5]

Table 6.4: ORR† by baseline disease characteristics, Primary and Extended Primary analysis sets

	Primary analysis set		Extended Primary analysis set	
Tumour type	**N**	**ORR % (95% CI)**	**N**	**ORR % (95% CI)**
Overall	55	75% (61, 85)	73	75% (64, 85)
ECOG				
0	24	92% (73, 99)	33	88% (72, 97)
1	27	63% (42, 81)	33	64% (72, 97)
2	4	50% (7, 93)	7	71% (29, 96)
Baseline stage				
Locally advanced	10	90% (55, 100)	13	85% (55, 98)
Metastatic	45	71% (56, 84)	60	73% (60, 84)
Number of prior regimens				
0	11	91% (59, 100)	15	87% (60, 98)
1-2	25	72% (51, 88)	35	71% (54, 85)
3 or more	19	68% (43, 87)	23	74% (52, 90)

CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; PR = partial response

† IRC Assessment
Data cut-off date: 19-February-2018

Source: [02.00.01_Vitrakvi_Note to Clinical Reviewer; Table 8, page 27, 28][5]

Table 6.5: Response to Larotrectinib† by patient age groups, Extended Primary analysis set

Patient Age	N	CR+PR	ORR, % (95% CI)
Pediatrics (<18 years)	21	19	90 (70, 99)
1 month to <2 years	9	9	100 (46, 100)
2 to <6 years	5	5	100 (46, 100)
6 to <12 years	4	2	50 (7, 93)
12 to <18 years	3	3	100 (29, 100)
Adults (≥18 years)	52	36	69 (55,81)
18 to <65 years	37	28	76 (59, 88)
≥65 years	15	8	53 (27, 79)

CI = confidence interval; CR = complete response; PR = partial response; IRC = independent review committee; ORR = objective response rate

† IRC Assessment
Data cut-off date: 19-February-2018

Source: [02.00.01_Vitrakvi_Note to Clinical Reviewer; Table 5, page 26][5]

Table 6.6: Response to Larotrectinib† by tumour histology, Extended Primary Analysis Set

Tumour Type	N	CR+PR	ORR, % (95% CI)
Overall	73	55	75 (64, 85)
STS	17	15	88 (64, 99)
Salivary gland	13	11	85 (55, 98)
IFS	10	9	90 (55, 100)
Colon	6	2	33 (4, 78)
Thyroid	6	6	100 (54, 100)
GIST	5	5	100 (48, 100)
Lung	4	3	75 (19, 99)
Melanoma	4	2	50 (7, 93)
Bone sarcoma	2	1	50 (1, 99)
Cholangiocarcinoma	2	0	0 (NC)
Appendix	1	0	0 (NC)
Breast	1	0	0 (NC)
CMN	1	1	100 (3, 100)
Pancreas	1	0	0 (NC)

CI = confidence interval; **CR** = complete remission; **CMN** = cellular congenital mesoblastic nephroma; **GIST** = gastrointestinal stromal tumor; **IFS** = infantile fibrosarcoma ; **NC** = not calculated; **ORR** = overall response rate

† IRC Assessment
Data cut-off date: 19-February-2018

Source: [02.00.01_Vitrakvi_Note to Clinical Reviewer; Table 6, page 26][5]

Table 6.7: Response to Larotrectinib† by NTRK Fusion and major NTRK isoforms, Primary, Extended Primary, and Integrated analysis sets

Fusion/Isoform Type	Primary Dataset N=	CR+PR	ORR, % (95% CI)	Extended Primary Dataset N=	CR+PR	ORR, % (95% CI)	Integrated Dataset N=
Overall	55	41	75 (61,85)	73	75	(64,85)	122
Fusion							
NTRK1	25	15	60 (39,79)	32	22	69 (50,84)	52
NTRK2	1	1	100 (3,100)	2	1	50 (1,99)	4
NTRK3	29	25	86 (68,96)	38	31	82 (66,92)	65
Review Ongoing or Not Determined				1	1	100 (3,100)	1
Isoform							
ETV6-NTRK3	28	24	86 (67,96)	35	39	83 (66,93)	52
TPM3-NTRK1	9	5	56 (21,86)	13	9	69 (39,91)	21
LMNA-NTRK1	5	2	40 (5,85)	8	5	63 (24,91)	11
IRF2BP2-NTRK1	2	2	100(16,100)				4
SQSTM1-NTRK1	2	2	100(16,100)				2

CI = confidence interval; CR = complete response; ORR = objective response rate; PR = partial response

† IRC Assessment
Data cut-off date: 19-February-2018

Source: [02.00.01_Vitrakvi_Note to Clinical Reviewer; Table 7, page 27][5]

Efficacy of larotrectinib in specific subgroups:

Soft tissue sarcomas (adult versus pediatric patients) – As of the 30-July-2018 data cut-off, 51 patients with sarcoma were included in the Integrated analysis. The majority (69%) of the sarcoma patients were under 15 years of age, and 51% of the patients were female. Thirty out of the 51 patients (59%) had a metastatic disease and 21 patients (41%) had locally advanced disease. Fourteen patients (27%) had received no prior systemic therapies at baseline; 17 patients (33%) had one prior treatment; 10 patients (20%) had two prior treatments, and 10 patients (20%) had received three or more previous therapies.[45]

Median duration of treatment in sarcoma patients was 9.4 months. The waterfall plot for the sarcoma subgroup, presented at the Connective Tissue Oncology Society Annual Meeting in November 2018, indicates that the ORR was comparable in the pediatric and adult sarcoma patients (Figure 6.7).[45]

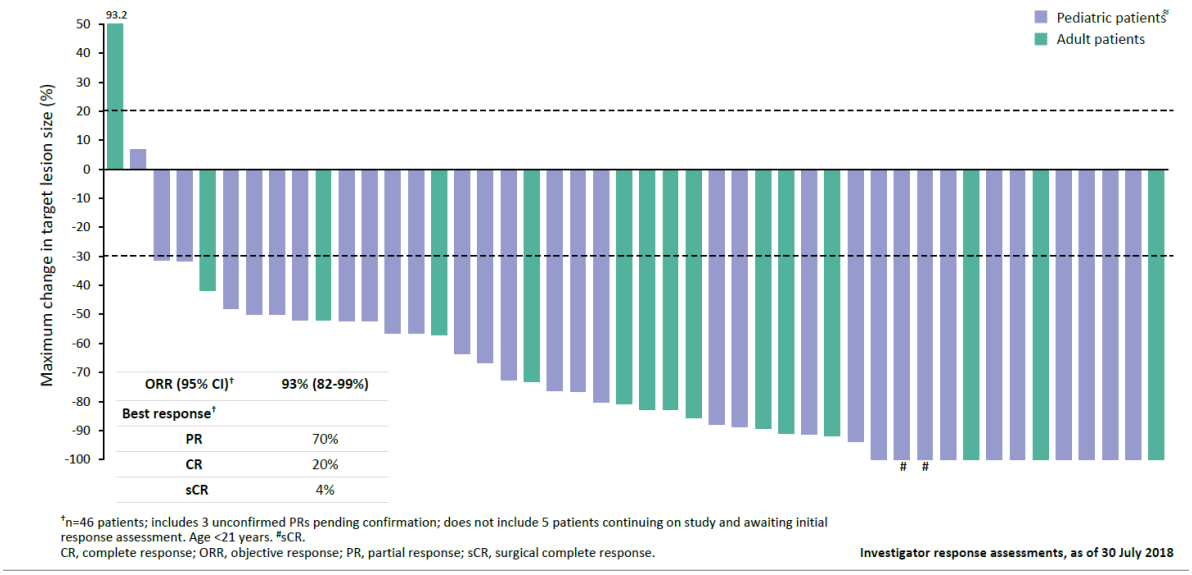
Primary CNS tumours - As reported in earlier in section 6.3.2.1, the inclusion criteria for the submitted pooled efficacy analysis excluded adult and pediatric patients who had primary CNS tumours. However, the efficacy of larotrectinib in patients with CNS tumours was analyzed separately, and the results of this analysis was presented in the American Society of Clinical Oncology (ASCO) 2019 Annual Meeting.[7] The analysis included patients with intracranial disease (primary CNS tumours or non-primary CNS solid tumors with brain metastases). All patients had a NTRK gene fusion that was determined by local molecular profiling. Objective responses were assessed by the investigator-assessed using RANO or RECIST (version 1.1) criteria.

As of the 30-July 2018 data cut-off date, 24 patients identified: six with non-primary CNS solid tumours and brain metastasis, and 18 with primary CNS tumours. The majority (83%) of patients

with primary CNS tumours were children (age range: 1-16 years). This may be related to the fact that the eligibility criteria for SCOUT trial included pediatric patients with primary CNS tumours (relapsed or refractory). Fourteen out of 18 patients with primary CNS tumours had evaluable data. The ORR was estimated to be 36% (95% CI 13%, 65%); with CR in two (14%), PR in three (21%), and stable disease in nine (64%) of the patients. The median PFS was 11.0 months (95% CI 2.8, not estimable). The treatment duration and best changes in tumour response in adult and pediatric patients with primary CNS tumours are illustrated in Figure 6.8.[7]

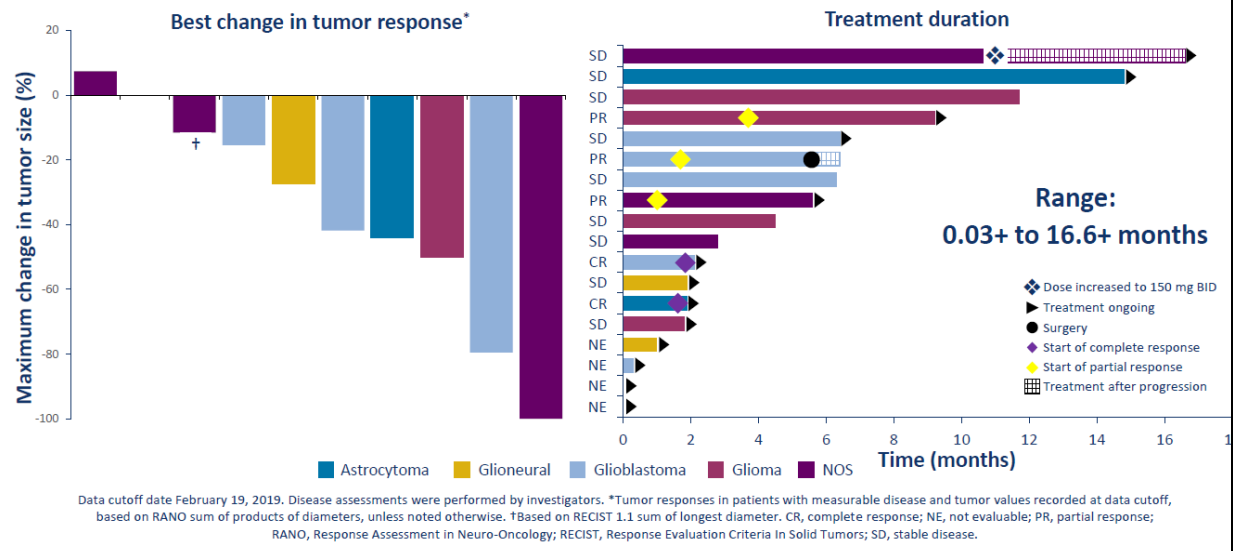
Larotrectinib formulation (oral solution versus capsules) – Based on the Submitter's response to the pCODR Checkpoint question, efficacy outcomes were available on the extended primary analysis population by oral solution versus capsule formulation. The majority of pediatric patients received the oral solution (n=16) with a small proportion receiving the oral capsule (n=5) while all adult patients received the oral capsule (n=52). The results (best overall response) were varied by a margin of 40% between the pediatric patients who received oral solution vs oral capsule. Given this margin may depend on a number of variables including tumour type, patient age and line of treatment, this result should be interpreted with caution, especially given the limited number of pediatric patients receiving the oral capsule. The results were somewhat similar between pediatric and adult patients who received the capsule formulation.[5]

Figure 6.7: Efficacy of larotrectinib in sarcoma patients harbouring NTRK gene fusions (Integrated analysis set)



Source: [Federman et al, CTOS 2018, oral presentation (slides provided by the Submitter)] ASCO annual meeting, May 31 - June 4, 2019, Chicago, IL, United States; Poster #293[45]

Figure 6.8: Treatment duration and response in patients primary CNS tumours harbouring NTRK gene fusions



Source: [Drilon et al, ASCO oral presentation (slides provided by the Submitter)] J Clin Oncol 37, 2019 (suppl; abstr 2006)[7]

Quality of Life[5]

Health-related quality of life (HRQoL) and health utilities were exploratory endpoints in the NAVIGATE and SCOUT trials. NAVIGATE used the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and European Quality of Life 5-Five Dimensions 5-Levels Health Questionnaire (EQ-5D-5L) for patients age 18 years and older, and the Pediatric Quality of Life-Core Module (PedsQL-Core) for patients aged 12 to 17 years. The SCOUT trial utilized Pediatrics Quality of Life – Core Module (PedsQL-Core). The HRQoL questionnaires were completed at the baseline and planned cycle visits (NAVIGATE: day 1 of cycles 3, 5, 7, 9, 11, 13, and every 3 cycles or months thereafter until disease progression; SCOUT: every cycle).[10]

The minimally importance difference was defined as a change in score of ≥10 points for EORTC QLQ-C30, ≥4.5 points for PedsQL-Core score, and ≥ 10 points for the EQ-5D-5L visual analog scale (VAS).[10]

Results from the analysis of patient-reported outcomes were presented in the ASCO 2019 Annual Meeting.[10] Based on this poster presentation, as of 30-July 2018 data cut-off date, 57 patients had completed questionnaires at baseline and at least one post-baseline follow up visit (40 adult patients for EORTC QLQ-C30/EQ-5D-5L and 17 pediatric patients ≥2 years of age for PedsQL).Eight adult patients had no baseline assessment: six patients had been enrolled prior the addition of the QLQ-C30 and EQ 5D-5L questionnaires to the study protocol (as part of a protocol amendment), instrument was not available in their native language for one patients and one patient was excluded for questionnaire completion errors.[10]

The numbers and proportions of patients with MID-improvement for the EORTC QLQC-30 (Global Health Score), EQ-5D 5L (VAS) and PedsQL (Total Score) are presented in Table 6.7.

Table 6.7: Best change from baseline in QoL scores (Navigate and SCOUT trials)

QoL questionnaire	EORTC QLQ-C30 global health score	EQ-5D-5L VAS health score	PedsQL (children ≥2 years old) total health score
Patients with baseline and ≥1 post-baseline assessment, N	40	40	17
Patients with best post-baseline score above baseline score, n (%)	28 (70)	29 (73)	15 (88)
Patients with best post-baseline score at or above MID* improvement, n (%)	24 (60)	24 (60)	13 (76)
Patients evaluable for sustained improvement (ie, with baseline and ≥2 post-baseline assessments), n	34	35	17
Patients with sustained improvement lasting ≥2 consecutive cycles, n (%)	14 (41)	18 (51)	11 (65)
Patients with sustained improvement lasting until the end of assessments, n (%)	9 (26)	11 (31)	8 (47)

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module; EQ-5D-5L, 5-level version of the EQ-5D; MID, minimally important difference; PedsQL, Pediatric Quality of Life Inventory; QoL, quality of life; VAS, visual analog scale.

*MID: ≥10 points for EORTC QLQ-C30 and EQ-5D-5L; ≥4.5 points for PedsQL.

Source: [Kummar et al, ASCO 2019 poster , Table 2 (provided by the Submitter)] ASCO annual meeting, May 31 - June 4, 2019, Chicago, IL, United States; Poster #293[10]

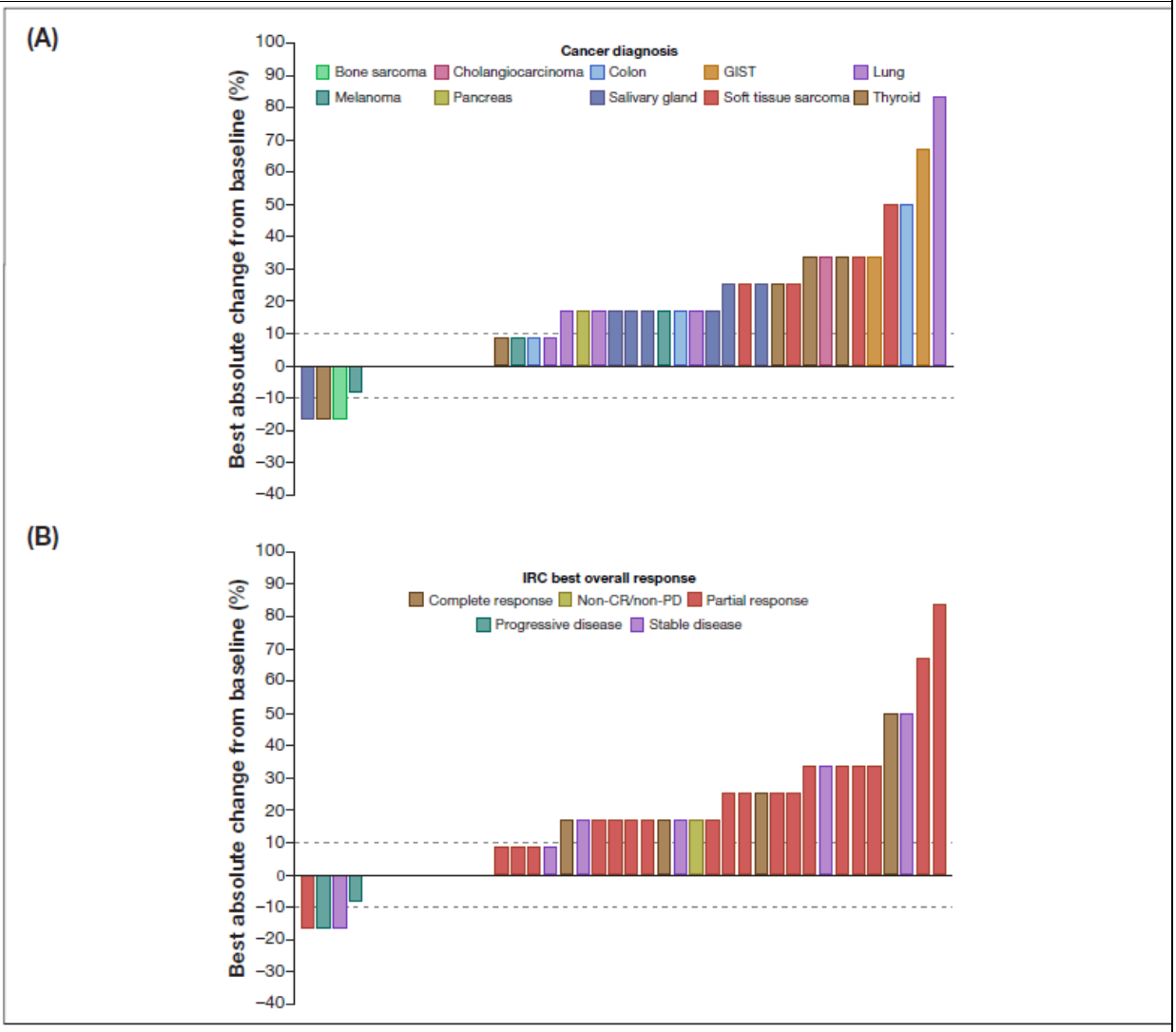
EORTC QLQ-C30 results:[10]

Of the 40 adult patients who completed EORTC QLQ-C30 questionnaire, 70% had and improvement in global health scores, with 60% reporting a best post-baseline score that reached or exceeded the MID of 10 points. Among evaluable patients, 41% had an improvement in EORTC QLQ-C30 global health score that lasted for at least two consecutive cycles (Table 6.7).

Figure 6.9 shows improvements EORTC QLQ-C30 global health score (best change from baseline) by tumour type and best overall tumour response. As shown, EORTC QLQ-C30 global health score improvements were reported for all tumor types (Figure 6.9A). Eighteen of 25 patients with partial tumor responses (RECIST v1.1) had a global health score improvement, 15 of which reached minimally important difference (MID) of 10 points. Of the six patients with stable disease, five had a global health score improvement, four of which reached MID. Among the five patients who had complete tumor responses, four had MID improvement. None of the three patients with progressive disease had global health score improvements (Figure 6.9B).

The median time to sustained improvement in EORTC QLQ-C30 global health score was 22.1 (95% CI 3.6, not estimable). The median duration of sustained improvement of those who improved in EORTC QLQ-C30 global health score was not estimable.

Figure 6.9: Best change from baseline in EORTC QLQ-C30 global health scores by (A) tumor type and (B) best overall tumor response



CR, complete response; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core Module; GIST, gastrointestinal stromal tumor; IRC, independent review committee; PD, progressive disease. Dotted lines indicate minimally important difference thresholds. A positive change from baseline indicates an improvement in the EORTC QLQ-C30 global health score.

Source: [Kummar et al, ASCO 2019 poster , Figure 1 (provided by the Submitter)] ASCO annual meeting, May 31 - June 4, 2019, Chicago, IL, United States; Poster #293[10]

EQ-5D-5L results:[10]

Of the 40 adult patients who completed EQ-5D-5L questionnaire, 73% had and improvement in VAS health score, with 60% reporting a best post-baseline score that reached or exceeded the MID of 10 points. Among evaluable patients, 51% had an improvement in VAS health score that lasted for at least two consecutive cycles (Table 6.7).

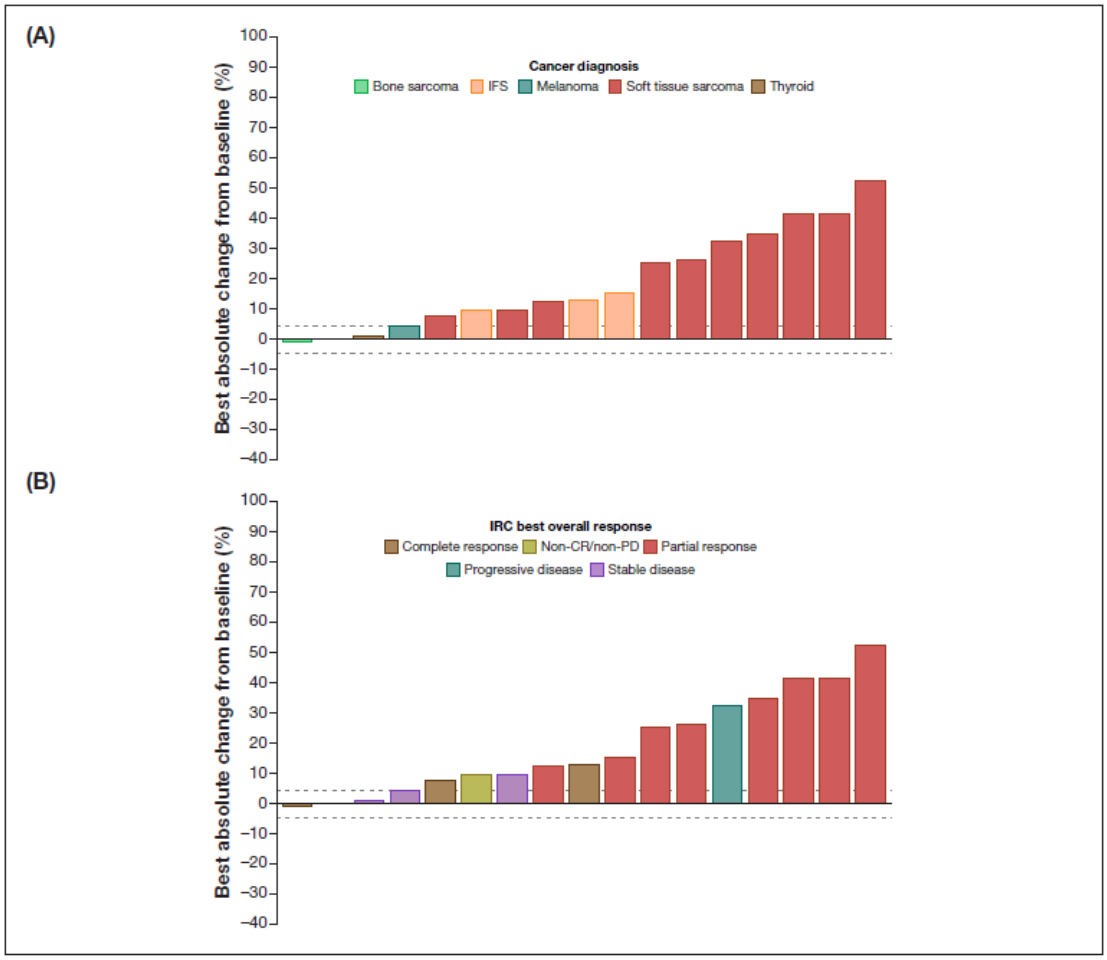
PedsQL-Core results:[10]

Of the 17 pediatric patients who completed PedsQL-Core questionnaire, 88% had improvement in PedsQL total scores, with 76% reporting a best post-baseline score that reached or exceeded the MID of 4.5 points. Among evaluable patients, 65% reported improvements that lasted for at least two consecutive cycles (Table 6.7).

Figure 6.10 shows improvements in PedQL total score by tumour type and best overall tumor response. As shown, PedQL total score improvements were observed across tumor types (Figure 6.10A). Eight of 9 patients with partial tumor responses had a MID improvement. Two of the three patients with complete tumor responses reached scores at or above MID improvement. In addition, all three patients with stable disease had improvements, with one patient reaching MID (Figure 6.10B).

The median time to sustained improvement in PedsQL total score was 3.9 months (95% CI 1.0, not estimable). The median duration of sustained improvement of those who improved PedsQL total score was not estimable.

Figure 6.10: Best change from baseline in PedsQL total scores by (A) tumor type and (B) best overall (RECIST v1.1) tumor response



CR, complete response; IFS, infantile fibrosarcoma; IRC, independent review committee; PD, progressive disease; PedsQL, Pediatric Quality of Life Inventory.
Dotted lines indicate minimally important difference thresholds. A positive change from baseline indicates an improvement in the PedsQL total score.

Source: [Kummar et al, ASCO 2019 poster , Figure 2 (provided by the Submitter)] ASCO annual meeting, May 31 - June 4, 2019, Chicago, IL, United States; Poster #293[10]

Harms Outcomes

As of the 30-July-2018 data cut-off date, a total of 207 patients were included in the safety analysis dataset. A summary of reported AEs is presented in Table 6.8. As the table shows, the majority of AEs were grade 1 or 2. Treatment-related Grade 3 or 4 AEs occurred in less than 5% of patients. The most common Grade 3/4 AEs included anemia, increase in liver enzyme (ALT and AST) levels, and nausea. Eleven out of the 122 patients (9%) in the Integrated analysis set required dose reductions due to AEs, and all maintained tumour regression on reduced dose.[5,6] Two patients discontinued larotrectinib due to an AE.[5]

Table 6.8: Summary of adverse events (≥15%) in patients with NTRK gene fusions from three larotrectinib trials, Safety data set (N=207)

	Treatment-emergent AEs (%)					Treatment-related AEs (%)		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Fatigue	18	15	3	–	36	<1	–	18
Dizziness	25	3	1	–	29	<1	–	21
Nausea	24	3	1	–	29	1	–	15
Constipation	22	5	<1	–	27	–	–	12
Anemia	10	7	10	–	27	2	–	11
ALT increased	17	5	3	<1	26	2	<1	21
AST increased	18	5	3	–	26	1	–	19
Cough	23	3	<1	–	26	–	–	1
Diarrhea	16	6	1	–	23	–	–	5
Vomiting	17	6	<1	–	23	–	–	10
Pyrexia	12	5	<1	<1	18	–	–	1
Dyspnea	10	6	2	–	18	–	–	1
Headache	13	4	–	–	16	–	–	4
Myalgia	12	3	1	–	16	<1	–	7
Peripheral oedema	12	4	–	–	15	–	–	7

- 11 (9%) of 122 patients with TRK fusion cancer required dose reductions – all maintained tumor regression on reduced dose
- 1 (<1%) of 122 patients with TRK fusion cancer discontinued larotrectinib due to an adverse event

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AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase

As of 30 Jul

Source: [Lassen ESMO 2018 presentation (provided by the Submitter)][6]

6.4 Ongoing Trials

No ongoing trials were identified as being relevant (fit the criteria outlined in the review protocol) to this review.

One other ongoing study was identified, which does not fit the review protocol, but which may provide important contextual information on the NTRK gene fusion. VOYAGER-1 is an ongoing retrospective cohort study that uses secondary data to study the patient characteristics and clinical outcomes in cancer patients with NTRK gene fusion and those in cancer patients without NTRK mutations who received current standard of care in a real-world setting. However, as the study is ongoing, outcome results are not currently available.[5] More details about the VOYAGER-1 study are summarized in Table 6.9:

Table 6.9: Characteristics of the VOAYGER-1 study	
Acronym	VOYAGER-1 : NTRK gene fusion-positive cancers: Patient profile and survival analysis in the real world setting using clinico-genomic data from Flatiron-FMI
Study type	retrospective cohort study
Research Question	What are the patient characteristics and prognosis for cancer patients with NTRK gene fusion and cancer patients without any NTRK gene mutations including gene fusion or other rearrangements?
objectives	Primary study objective: • To evaluate overall survival (OS) from date of NGS report for cancer patients with NTRK gene fusion and cancer patients without NTRK gene mutations

	(including gene fusion or other rearrangements) who received current standard of care Secondary study objectives: • To describe frequency of cancer patients with NTRK gene fusion by tumor type among patients who received NGS test • To describe frequency of cancer patients with other NTRK gene rearrangements by tumor type among patients who received NGS test • To describe patient characteristics of patients with NTRK gene fusion, or other NTRK gene rearrangements, or no NTRK mutations • To describe treatment patterns in cancer patients with NTRK gene fusion, or other NTRK
population	patients in the Flatiron Health database who underwent comprehensive genomic profiling including NTRK gene fusion diagnosis by FMI as part of routine, real-world care from January 1, 2011 to July 31, 2018.
Cohorts	• **Cohort 1: Cancer patients with NTRK gene fusion from NTRK Rearranged CG database (n=29 with different tumor types)** • Cohort 2_All: Cancer patients without any NTRK gene mutations including NTRK gene fusion or rearrangements, or other alterations (n = 14,184 for tumor types seen in Cohort 1). • Cohort 2_Matched: Cancer patients without NTRK gene mutations who are matched with cohort 1 based on baseline patient characteristics (n > 100 with 4:1 match) • Cohort 3: Cancer patients with other NTRK gene rearrangements (n=63) • Cohort 4: Cancer patients with other NTRK gene alterations (eg, amplification, point mutation, etc. N=3,600) Note: Cohort 1 is relevant to the pCODR review
Study results	Not available
Country(s) of study	USA
Funding	Bayer AG, Germany
Notes	Cohort 1 (cohort of NTRK gene fusion patients) is relevant to the pCODR review According to the study protocol, a broad range of tumor types may be included in this cohort and "patients with different tumor types will vary substantially in both prognosis and treatment options". To address the heterogeneity, patients will be matched on tumor type. However, it is predicted in the study protocol that "matching process and other statistical adjustment may be compromised by the limitation of data availability".
NGS = Next-Generation Sequencing**; NTRK =** Neurotrophic Tyrosine Receptor Kinase; **USA** = United States of America **Source**: [VOYAGER-1 study protocol version 1.1, 22-March-2019 (provided by the Submitter)][5]	

7 SUPPLEMENTAL QUESTIONS

The following supplemental question were identified during development of the review protocol as relevant to the pCODR review of larotrectinib (Vitrakvi) for NTRK positive solid tumours.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Prognostic relevance of the NTRK fusion protein in patients with solid tumours

7.1.1 Objective

The objective of this section was to identify any information regarding the prognostic relevance of the NTRK fusion proteins. A literature search was conducted retrieving a total of eight relevant published articles/abstracts. The retrieved articles were analysed and organized into common themes.

7.1.2 Findings

A literature search was conducted using key search terms (NTRK gene fusions OR Neurotrophic Tyrosine Receptor Kinase) within the title or abstract through the Medline and Embase databases. A total of 49 search items were retrieved from the literature search. All items were reviewed by one reviewer at the title and abstract level. Twenty-nine full text articles were reviewed by one individual. Two of the full-text primary research publications were found to be the same article, Farago et al.[77] and Farago et al.,[78] therefore only the most recent publication[78] was reported here. Seven articles were chosen to be summarized in this section, including one abstract[79] and six primary research articles.[21,78-83] No formal PICO were identified a-priori as this literature search was meant to beencapsulating of any literature potentially relevant to the prognostic impact of the NTRK gene fusion. However, in general, studies chosen for consideration were limited to non-animal studies, as the review team's goal was to identify the prognostic relevance of the NTRK gene fusion protein in humans. In addition, in vitro studies examining the NTRK gene fusion protein were also excluded.

None of the retrieved articles addressed the impact of the NTRK gene fusion on patient prognosis or important patient outcomes such as survival. Therefore, based on the literature search results identified, the prognostic relevance of the NTRK gene fusion remains unclear.

The articles retrieved were however organized into themes that discussed factors relevant to the presence of the NTRK gene fusion and characteristics of patients with the NTRK fusion protein. These are discussed below.

7.1.3 NTRK gene fusions have a low frequency of occurrence

All the literature results indicated that the NTRK gene fusion has a low frequency of occurrence among cancer types. Gatalica et al.[79] analyzed gene fusions within 11,116 tumour samples and identified 23 validated cases with an NTRK gene fusion. An updated analysis also by Gatalica et al.[21] analyzed samples from 11,502 patients, of which 31 (0.27%) had NTRK fusions. Farago et al.[78] reached out to physicians across 47 institutions in the United States for data on patients with NSCLC harbouring an NTRK gene fusion. Information was not available on when the data collection was conducted nor the total number of patient sample screened. Of all institutions sampled by Farago et al. only 11 patients contained verified TRK fusions containing the kinase domain.

While the frequency of occurrence of the NTRK fusion protein is low, it seems to be more prevalent among less frequently occurring cancers such as central nervous (CNS) cancers compared to more common cancers such as lung cancer. Out of 23 samples with confirmed NTRK gene fusion in the abstract by Gatalica et al.,[79] 11 of the confirmed cases were among patients with CNS malignancies, most of them being glioblastoma; the remaining 12 cases were found in a range of non-CNS cancers, including carcinomas of the respiratory tract (n=3), colon (n=2), thyroid (n=2), skin, cervix, uterus and soft tissue (n=1 each), and one carcinoma of unknown primary site. Another study by Marchetti et al.[82] also conducted gene profiling of 95 patients with neuroendocrine tumours of the lung, and 443 patients with NSCLC. Mutations of NTRK occurred in 9.5% (n=9) of neuroendocrine tumours, while there was no presence of mutations among patients with NSCLC. All nine of the mutations occurred in patients with large cell neuroendocrine carcinomas.[82] Pavlick et al.[83] conducted genetic profiling of 2,031 tumour samples from pediatric and young adult patients, which included those under 20 years of age; of this sample 0.44% (n=9) of patients were identified as harbouring the NTRK gene fusion.

For some types of cancers, the NTRK fusion protein seems to have a lack of clinical significance. Vranic et al.[81] conducted genetic profiling of 20 surgical tumour samples of neuroendocrine carcinomas (NEC) of the breast. In all cases, there was no presence of the NTRK gene fusion. The authors concluded that patients with breast NEC would be unlikely to benefit form NTRK inhibitors, such as larotrectinib or entrectinib.

Table 8.1: Summary of studies assessing frequency of NTRK gene fusions

Study	Sample size of patients screened for the NTRK gene fusion N	Identified NTRK gene fusion cases N (%)
Gatalica et al.[79]	11,116 patients	23 (0.21)
Gatalica et al.[21]	11,502 patients	31 (0.27)
Farago et al.[78]	Physicians from 47 institutions	11*
Marchetti et al.[82]	95 patients with neuroendocrine tumours of the lung 443 patients with NSCLC	9 (9.5) 0
Pavlick et al.[83]	2,031 tumour samples from pediatric and young adult patients	9 (0.44)
Vranic et al.[81]	20 surgical tumour samples of neuroendocrine carcinomas of the breast	0
*Information was not available on the numbers of patients screened to identify n=11 from within the 47 institutions		

7.1.4 Co-existing genetic alterations

The literature search also identified that the presence of NTRK gene fusion proteins may co-occur alongside other actionable targets, such as PD-L1. Gatalica et al.[79] found that 4/23 cases of patients with an NTRK gene fusion also had expression of the PD-L1 gene alteration. The four cases with co-expression of NTRK and PD-L1 were patients with colorectal and lung cancers. The updated publication by Gatalica et al.[21] reported that 7/31 (23%) confirmed NTRK fusion positive cases also had PD-L1 expression. One patient also expressed EGFR and MET amplification, and one patient also expressed VEGFR2 gene amplification and mutation. NTRK fusions were most frequently seen in concurrence with TP53, PTEN, and PIK3CA mutations. Lastly, mutational burden was highest in two microsatellite instability high cases, one colorectal carcinoma case (TPM3-NTRK1), and one cancer of unknown primary case (ETV6-NTRK3).

7.1.5 NTRK expression occurs across a wide range of patient characteristics

Among a sample of eleven lung cancer patients with the NTRK gene fusion protein, patients varied across age, sex and smoking status.[78] The histological features of the NSCLC patients also varied, with nine patients diagnosed with adenocarcinoma, one with squamous cell carcinoma and one with neuroendocrine carcinoma. Even amongst patients with adenocarcinoma, patients were diagnosed with a range of histological subtypes. The authors determined that there could be no discernable clinical or pathological features of NTRK fusion positive NSCLC patients, and recommended screening all NSCLC patients with the NTRK gene fusion. However, limitations of the sample were acknowledged, including a retrospective study design, recruitment of patients across multiple institutions, and the small study cohort (n=11).[78]

Among a sample of nine pediatric and young adult patients, ages ranged between less than one year to 20 years of age and included five females and four males. The diagnoses of these patients varied from leukemias, solid tumours and primary CNS tumours.[83] Like the sample of lung cancer patients, the pediatric cohort was small, limiting the interpretability and generalizability of the findings.

Marchetti et al.[82] detected NTRK mutations among nine patients with large cell neuroendocrine carcinomas of the lung. The nine patients varied across age (mean:64.4 years, standard deviation:11.8), sex (male: 78%, n=7), tumour size (T1: 33%, n=3; T2:67%, n=6), node status (N0:67%, n=6; N1: 22%, n=2; N2: 11%, n=1), disease stage (stage I: 67%, n=6; stage II: 22%, n=2; stage III: 11%, n=1), and histological subtype (pure large cell neuroendocrine carcinoma: 67%, n=6; combined large cell neuroendocrine carcinoma: 33%, n=3).

A study by Ge et al.[80] collected tumours samples from 57 patients diagnosed with ovarian cancer for primary treatment. These 57 patients also varied on platinum-resistance or sensitivity, time to recurrence, International Federation of Gynaecology and Obstetrics (FIGO) stage, differentiation of tumour, pathological subtypes, residual tumours, receipt of neoadjuvant therapy, and median survival time. While patients exhibited a wide range of clinicopathological characteristics, most patients were FIGO stage III (n=48), had poorly differentiated tumours (n=42), had serous adenocarcinoma (n=36), and residual tumours <1cm (n=39).[80]

7.1.6 Limitations

None of the articles retrieved through the literature search spoke directly about the prognostic relevance of the NTRK gene fusion. The retrieved articles provided some insight regarding patient or gene mutation characteristics, but they did not comment on the impact of the NTRK fusion protein on outcomes relevant to patients. Instead, articles retrieved were organized into themes that addressed the incidence of the NTRK gene fusion and characteristics of patients in which the NTRK fusion protein is detected.

All primary studies retrieved through the literature search were retrospective in design. In cases where presence of the NTRK gene fusion were verified, sample sizes were small, making the generalizability of findings difficult to determine. Some studies were able to screen over 500 tumours to show that the frequency of NTRK gene fusions is generally low. The observations reported in these studies must also be interpreted with caution due to small sample sizes of NTRK positive patients identified among the large number of patient samples screened.

Overall, any observations retrieved from the literature search should be interpreted with caution as the relevance of the gene mutation on prognosis and patient outcomes is still

unclear. Despite this, the studies identified seemed to generally support the use of TRK inhibitors for patients with expression of the NTRK gene mutation.

7.1.7 Additional evidence identified by the Sponsor

After the posting of the pERC initial recommendation on larotrectinib within the indication under review, the Sponsor provided feedback specifically addressing the prognostic relevance of the NTRK fusion protein as an oncogenic driver responsible for both the initiation and maintenance of cancer. However, it should be noted that the CADTH review team had asked the Sponsor on multiple occasions to provide evidence regarding the prognostic impact of the NTRK gene fusion on patients, and the Sponsor had indicated that there was no evidence within the literature to support this assumption. During feedback, the Sponsor provided seven citations[39,84-89] as evidence suggesting the relevance of the NTRK gene fusion protein as a prognostic factor in cancer. The Review Team screened the citations provided and noted that one of the seven were retrieved through the literature search conducted by CADTH for this section[39], a citation which was subsequently excluded at the screening stage of the CADTH literature review as the publication was an animal study. Although the remaining six citations would have been excluded from the CADTH literature search given their use of animal models, based on the terminologies used for the search, these 6 citations would not have been captured by the CADTH literature search. The references provided by the Sponsor are briefly summarized below.

Four of the articles cited by the Sponsor in the feedback discussed the significance of ETV6-NTRK as a crucial link between signalling pathways and abnormal cell cycle progression through in vitro models.[84,85,88,89] Wai et al.[89] showed that ETV6-NTRK3 transforms cells, and requires a dimerization domain and a functional protein tyrosine kinase (PTK) domain for transformation activity. Tognon et al.(2001)[85] focused on the roles of certain pathways (Ras-Erk1/2 and PI3K-Akt) in ETV6-NTRK3 transformation, and whether pharmacological inhibition could block ETV6-NTRK-mediated transformation. Park et al.[84] analysed transcription alterations in mice fibroblasts transduced with the ETV6-NTRK fusion to identify mechanisms involved in ETV6-NTRK mediated tumorigenesis. An article by Cetinbas et al.[88] also aimed to determine the mechanism of the NTRK mutation; specifically whether electrostatic interactions involving Lys-99, which is related to the formation of a salt bridge relevant to the sterile alpha-motif (SAM) domain of the ETV6 transcription factor, is important to activity of the ETV6-NTRK3 fusion in cells.

The evidence provided thus far suggests that the NTRK gene fusion protein, specifically the NTRK3 gene, has oncogenic potential through activation of certain pathways and other related biological mechanisms. However, the data provided by Wai et al.[89], Tognon et al. (2001)[85], Park et al.[84] and Cetinbas et al.[88] used in vitro models, or animal models with mice. While mice models may be used to predict the applicability of genetic mutations in humans, results require validation in humans.

Two of the citations provided by the Sponsor examined IGF1R inhibition as a mechanism for targeting carcinogenesis related to the ETV6-NTRK3 gene fusion.[86,87] Tognon et al. (2011)[86] sought to explore the role IGF1R signalling in ETV6-NTRK3 breast cell oncogenesis through in vivo and in vitro models. Overall, Tognon et al. (2011)[86] concluded that IGF1R/insulin receptor inhibitors would be useful in treating ETV6-NTRK driven breast cancers. Tognon et al. (2018)[87] were able to demonstrate that IGF1R inhibition results in ubiquitylation and degradation of the ETV6-NTRK3 oncogene protein through a reversible mechanism.

One of the citations provided by the Sponsor was a study in humans.[39] As mentioned, Tognon et al. (2002)[39] was previously excluded during the abstract screening stage of the literature search. As the article was considered relevant by the Sponsor, the review team obtained the

full-text of this publication, and noted that the authors, Tognon et al. (2002)[39], related their study findings to human tumour samples; the publication by Tognon et al. (2002)[39] is briefly summarized here. Tognon et al. (2002)[39] suggested that ETV6-NTRK3 fusion transcripts may be expressed in human breast cancer patients based onone single six-year-old female patient diagnosed with invasive breast adenocarcinoma. Tognon et al. (2002)[39] stated that the histopathological features of the six-year-old patient's tumour were similar to those of a secretory breast carcinoma (SBC). Therefore, Tognon et al. (2002)[39] aimed to demonstrate that expression of the ETV6-NTRK3 gene helps to characterize SBC and transforms mammary epithelial cells. Tognon et al. (2002)[39] were able to confirm presence of the ETV6-NTRK3 gene fusion by conducting FISH and PCR analyses on frozen tumour tissue from the six-year old patient. Tognon et al. (2002) also assessed for presence of ETV6-NTRK expression in 12 other breast cancer patients were SBC was the predominant or only histological component for the purpose of confirming whether ETV6-NTKR3 expression is a generalized finding in SBC. Out of 12 cases, 11 patients also had confirmed expression of ETV6-NTRK3 fusion transcripts. Tognon et al. (2002)[39] suggest that the ETV6-NTRK3 gene fusion is a non-random rearrangement in SBC. Using mice cells, Tognon et al. (2002)[39] found that cells expressing ETV6-NTRK3 had transformative activity in epithelial cells, and suggested a causal link between ETV6-NTRK gene fusion expression and oncogenesis in human SBC.

7.1.8 Summary

Overall, the literature search did not identify any relevant information that spoke directly to the prognostic relevance of the NTRK fusion protein on various types of cancers. The literature search resulted in seven primary full-text articles, one abstract, and an additional article identified through a reference list. In general, the identified literature reported that the occurrence of the NTRK gene fusion is low although it seems to be more prevalent among less common cancers, such as those presenting in the CNS, and less prevalent among more common cancer types, such as lung cancers. Patient characteristics of those carrying the NTRK gene fusion were found to vary in age, sex, and various relevant diagnostic categories. Two publications commented on the co-occurrence of targetable mutations alongside the NTRK gene fusion, such as PD-L1. While the literature search indicated some potential patterns across patients with presence of an NTRK gene fusion, they could not indicate how the factors affect the prognosis of patients and outcomes. For example, it is unclear how co-existing gene mutations will affect the prognosis of a patient; however, Gatalica et al.[21] stated that with the presence of multiple oncogenic drivers, opportunities for combination therapies may present themselves in the future. In addition, given the wide range of patients that the NTRK gene fusion is detected among, it is not clear which patients may be more likely to have an NTRK gene fusion. While some characteristics of patients with NTRK gene fusions were analyzed, it is unclear how these characteristics and presence of the gene fusion will affect patients disease prognosis. A review article by Chetty et al.[22] acknowledged that while the gene fusions are the main mechanism by which the oncogenic potential of the NTRK1-3 genes are unleashed, the mechanisms by which the NTRK mutations result in carcinogenesis and progression of a patients' cancer are unknown. Overall, while the identified literatures generally agreed that the NTRK gene fusion is an oncogenic driver in various cancers, the literature search did not identify any relevant data to directly indicate how the presence of the gene mutation affects a patient's prognosis.

Most articles referenced by the Sponsor in response to the pERC initial recommendation examined the ETV6-NTRK3 gene fusion in cell cultures and mouse models. Transgenic mice models have been used in cancer research to study carcinogenesis, tumour pathogenesis, and development of resistance to therapy. Mouse models have been useful in researching the interactions between tumours and their environments, and have aided in exploration of precise individualized cancer therapy.[90] However, it is important to understand the limitations

of analysing genetic insertions or deletions in culture, or mouse models to understand cancer biology in humans as animals models do not fully reveal the complexity of the tumours environment in humans. Of the articles provided by the Sponsor in response to the pERC initial recommendation, only one related in vitro and in vivo results of the study to human patients.[39] Tognon et al. (2002)[39] were able to confirm presence of the ETV6-NTRK3 fusion in a small sample of patients with SBC, and suggested a causal link between expression of ETV6-NTRK3 and oncogenesis in human SBC. However, Tognon et al. (2002)[39] did not provide details regarding patient outcomes and how presence of the ETV6-NTRK3 gene fusion impacted cancer prognosis.

8 COMPARISON WITH OTHER LITERATURE

8.1 Testing for Neurotrophic Receptor Tyrosine Kinase (NRTK) Gene Fusion.

8.1.1 Currently Available Testing Approaches for Solid Tumours

In the Canadian setting, while molecular testing is being performed on a number of solid-organ and soft tissue tumours (colorectal carcinoma, melanomas and gastrointestinal stromal tumors (GISTs)), RNA-based NGS has only been incorporated into testing for lung carcinomas and sarcomas. While it expected that NGS testing, including RNA-based fusion analysis will expand over the next 12 – 24 months for lung and sarcomas, it cannot be assumed that fusion analysis is routinely done at the current time. While NGS is used for melanoma, GIST, and CRC, the NGS is DNA based. Testing for the NTRK fusion protein requires RNA based NGS testing thus for these cancers either an alternative testing platform or separate testing would be required.

8.1.2 NTRK Fusion Protein Frequency of Occurrence

NTRK fusions have a low frequency of occurrence, involving <1% of pediatric and adult tumours. Molecular testing is more widely available and incorporated into pediatric tumour testing. Different studies have reported varying frequencies which may be explained by the number of patients screened and NTRK fusion detection techniques. While rare, infantile fibrosarcoma (IFS)[38] and congenital mesoblastic nephroma[23] have a high (>90%) frequency of NTRK fusions, making NTRK testing a key diagnostic marker in these patients.

In the adult and pediatric population, salivary gland mammary analogue secretory carcinomas[40] and secretory mammary carcinomas[23] are associated with a high-likelihood of NTRK fusions. Outside of these rare tumours NTRK fusions are rare.

	Annual incidence (Canadian)	Low estimated freq	High estimated freq
aSTS	1,130	0.5%	2.0%
NSCLC	24,310[&]	0.1%	3.0%[32]
Thyroid	7,100[43]	1.5%*	12.0%*
CRC	26,800[43]	0.2%	2.0%
Melanoma	7,200[43]	0.2%	2.0%
Glioblastomas/ Astrocytoma	1505[91]	0.4%	3.1%
Cholangiocarcinoma	128[92]	--	3.6%
Pediatric Gliomas	475[91]	--	7.1%

* The higher incidence of the NTRK fusion protein in thyroid cancer is based on studies using metastatic / recurrent papillary thyroid carcinoma.
[&]NSCLC represents approximately 85% of all cases of lung cancer cases annually (28,600[43])
Estimates taken from Vaishnavi 2015[23] unless otherwise stated

8.1.3 Testing Approaches for NTRK Fusion Protein

NRTK gene fusion can be determined by a number of methods, including RNA-based next-generation sequencing (NGS) or fluorescent in-situ hybridization (FISH). Both methods were recognized by the U.S. Food & Drug Administration (FDA) as methods to identify patients with gene fusions.[93]

Given the low frequency of occurrence of NTRK fusions in most tumours, and lack of RNA-based NGS for most solid organs, NTRK immunohistochemical testing is an accepted method to screen cancers for NTRK fusions. While there is a current national group looking at the best application for immunohistochemistry to identify patients with NTRK fusions (CanTRK), there are no population-based studies looking at the routine implantation of NTRK immunohistochemistry. While awaiting the results of CanTRK, based on limited studies the immunohistochemical testing has an estimated sensitivity of 97% and an estimated specificity of 98%.[94] As immunohistochemistry is not specific, confirmation of an NTRK fusion requires molecular confirmation, with RNA-based NGS panel testing is the preferred method for confirming NTRK fusions. Immunohistochemistry is not a suitable screening tool for CNS based tumours or smooth muscle tumours, molecular testing is needed to detect NTRK fusions in tumours from these sites.

8.1.4 Proposed testing algorithm to identify patients with NTRK fusions[95]

For cases with a high likelihood of NTRK fusion (infantile fibrosarcoma, congenital mesoblastic nephroma, mammary analogue secretory carcinomas and secretory mammary carcinomas) or cases in which immunohistochemical staining is not appropriate (CNS tumours, smooth muscle tumours) RNA-based NGS testing should be performed.

For tumours in which NGS panel are being used as part of clinical practice (such as lung adenocarcinoma and sarcomas), NTRK fusions should be incorporated as part of the biomarker panel testing.

For all other tumours (including tumours with panel testing which did not include NTRK), NTRK immunohistochemistry should be done, followed by RNA-based NGS to confirm the presence of a gene fusion. There is a pan-Canadian group currently investigating the immunohistochemical assessment of NTRK (Can-TRK), when available the findings from this group will allow for the better modelling of immunohistochemical results. Based on previous studies looking at the sensitivity and specificity of NTRK immunohistochemistry and the estimated frequency in the general population, 3 – 5% of tumours would require fusion analysis to confirm the presence of an NTRK fusion.

NTRK testing should be incorporated into a comprehensive approach to biomarker testing. For the majority of lung carcinomas, pediatric tumours and sarcomas this testing is done at the time of diagnosis. For other tumours, such as melanomas, biomarker testing is done on all advanced tumours, while for colorectal cancer and thyroid cancer the testing is done at time of recurrence or progression on therapy.

For adult sarcoma and lung adenocarcinoma, NTRK testing should be built into the NGS testing for other fusion products, as a result IHC screening is not necessary.

Estimates for the volume of colorectal cancers and melanomas which would require screening for NTRK are based on the percentage of cases which have molecular testing done in the Ontario experience. In these tumours molecular testing is incorporated once tumours fail standard therapy (for CRC) or when chemotherapy is being used as part of treatment (melanoma).

8.1.5 Turn-Around-Time (TAT)

The typical TAT for immunohistochemical testing ranges from 2 – 5 calendar days. The TAT for NGS testing, including RNA-based NGS testing ranges from 2 – 4 weeks, depending on the scope of testing.

Given the TAT for molecular analysis, NTRK testing should be incorporated as part of any initial biomarker investigation or at the time of recurrence/ resistance to initial chemotherapy.

8.1.6 Costs of Testing

Although there are variations in the cost of testing across provinces, the estimated costs for immunohistochemistry is $50 for technical component and $15.60 for the professional interpretation / reporting (professional fee is from the OHIP schedule of benefit for the interpretation of immunohistochemical markers).

The estimated cost for the RNA-based NGS panel would be $1000. There is no professional fee for the interpretation / reporting of molecular panels currently in the schedule of benefits, based on the reimbursement of other molecular interpretation fees, the profession interpretation / reporting cost would be estimated to be $40.

8.1.7 Estimated Canadian Test Volume

There is no prospective, population-based study to accurately determine the testing volume. Currently available studies are based on sub-select patient volumes. When taking a prospective approach to identifying patients with NTRK fusions it is assumed that NTRK fusion testing would be incorporated into an algorithm where all molecular biomarkers are done in a comprehensive manner.

Ontario has been tracking molecular testing volumes as part of its reimbursement model. Using the Ontario experience, in 2018/2019 molecular testing is performed on 78% of lung cancers, 48% of colorectal cancers and 44% of melanomas.

Molecular analysis of thyroid cancers has not entered into general practice in Canada. NTRK testing is only indicated in recurrent / resistant papillary thyroid cancer (an estimated 4 – 7% of thyroid cancers).

The estimated Canadian testing volume was done using the Ontario experience with molecular testing and the estimated volume of recurrent / resistant thyroid. The estimated NGS testing volume was done using the highest frequency for NTRK fusions from the table below and an estimated IHC sensitivity of 98% and specificity of 97%.

Tumours with a high-frequency of having a NTRK fusion (an estimated volume of 20 / year) go straight to NGS testing. These tumours have been excluded from the estimates below.

	Canadian Annual Incidence	Estimated Testing Volume (IHC)	Estimated Testing Volume (NGS)
Adult STS	1,130 (Ref)	-	950
NSCLC	24,310[¢]	-	18,966
Thyroid	7,100[43]	550	80
Pediatric STS	125[91]	100	5
CRC	26,800[43]	12865	630
Melanoma	7,200[43]	3240	160
Astrocytoma / Glioblastomas	1505[91]	-	1505

Estimates taken from Vaishnavi 2015[23] unless otherwise stated
[¢]NSCLC represents approximately 85% of all cases of lung cancer cases annually (28,600[43])

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lung, Breast, Gastrointestinal, Pediatric, Sarcoma and Endocrine Clinical Guidance Panels (CGP) and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on larotrectinib (Vitrakvi) for NTRK positive solid tumours. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH 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 Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Clinical Guidance Panel for the current review is comprised of four medical oncologists and one pathologist. The panel members were selected by the pCODR program, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

Literature Search Methods

1. Literature search via Ovid platform

Database(s): Cochrane Central Register of Controlled Trials (CENTRAL); Embase (1974 to present); MEDLINE All (1946 to present)

#	Searches	Results
1	(larotrectinib* or Vitrakvi* or ARRY-470 or ARRY470 or LOXO-101 or LOXO101 or PF9462I9HX).ti,ab,ot,kf,kw,hw,rn.	203
2	1 use medall	44
3	1 use cctr	5
4	Larotrectinib/ or (larotrectinib* or Vitrakvi* or ARRY-470 or ARRY470 or LOXO-101 or LOXO101).ti,ab,kw,dq.	202
5	4 use oemezd	154
6	5 and (conference review or conference abstract).pt.	52
7	limit 6 to english language	52
8	limit 7 to yr="2014 -Current"	51
9	5 not (conference review or conference abstract).pt.	102
10	2 or 3 or 9	151
11	limit 10 to english language	151
12	remove duplicates from 11	110
13	8 or 12	161

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#3	Search #1 AND #2 Filters: English	2

Search	Query	Items Found
#2	Search publisher[sb]	538765
#1	Search (larotrectinib*[tiab] OR Vitrakvi*[tiab] OR ARRY-470[tiab] OR ARRY470[tiab] OR LOXO-101[tiab] OR LOXO101[tiab] OR PF9462I9HX[tiab]	43

3. **Cochrane Central Register of Controlled Trials (CENTRAL)**
   (searched via Ovid)

4. **Grey literature search via:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Vitrakvi/larotrectinib, NTRK gene fusion +

Select international agencies including:

US Food and Drug Administration (FDA)
https://www.fda.gov/

European Medicines Agency (EMA)
https://www.ema.europa.eu/

Search: Vitrakvi/larotrectinib, NTRK gene fusion +

Conference abstracts:

American Society of Clinical Oncology (ASCO)
https://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Vitrakvi/larotrectinib, NTRK gene fusion + — last five years

APPENDIX B: Detailed Methodology of Literature Review

Literature Search Methods

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[96]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Vitrakvi/larotrectinib.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of August 1, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[97] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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