CADTH

CADTH REIMBURSEMENT REVIEW

Patient Input

LAROTRECTINIB (Vitrakvi)

(Bayer Inc.)

Indication: Solid tumours with NTRK gene fusion

CADTH received patient input from:

Canadian Breast Cancer Network

Canadian Cancer Survivor Network, Advocacy for Canadian Childhood Oncology Research Network, Colorectal Cancer Resource & Action Network, GIST Sarcoma Life Raft Group Canada (Joint Submission)

Colorectal Cancer Canada

Lung Cancer Canada

Sarcoma Cancer Foundation of Canada

December 4, 2020

CADTH

CADTH Drug Reimbursement Review
Patient Input Template

Name of the Drug and Indication	Larotrectinib/Vitrakvi 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.
Name of the Patient Group	**The Canadian Breast Cancer Network**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

The Canadian Breast Cancer Network (CBCN) is a leading, patient-directed, national health charity committed to ensuring the best quality of care for all Canadians affected by breast cancer through the promotion of information, education and advocacy activities. www.cbcn.ca

The Canadian Breast Cancer Network is committed to adhering to a Code of Conduct Governing Corporate Funding as outlined at www.cbcn.ca .

2. Information Gathering

Information for this submission was collected via:

CBCN's 2017 Survey of Metastatic Breast Cancer Patients – Results were published in "Breast Cancer: The Lived Experience" report that was released in October 2018

This online survey collected comprehensive data from 180 Canadians living with metastatic breast cancer. Survey questions comprised of a combination of scoring options and free form commentary. It is unknown whether or not patients who participated in this survey have experience with the treatment under review. Patients were contacted through CBCN's patient network, website and social media.

CBCN's 2012 Metastatic Breast Cancer Patient and Caregiver Survey Report: An online survey was distributed to patients living with metastatic breast cancer and their caregivers. No patients surveyed had experience with the treatment under review. Survey questions comprised of a combination of scoring options and free form commentary. Patients were contacted through the membership databases of CBCN and other patient organizations.

-71 patients participated in the survey
-16 caregivers participated in the survey

Printed sources: A review was conducted of current studies and grey literature to identify issues and experiences that are commonly shared among many women living with metastatic breast cancer.

3. Disease Experience

Metastatic breast cancer is the spread of cancerous cell growth to areas of the body other than where the cancer first formed. It is most commonly spread to the bones, but can include the lungs, liver, brain and skin.

Triple-negative breast cancer (TNBC) is breast cancer that is estrogen-receptor-negative, progesterone-receptor-negative and HER2-negative. Accounting for 12-17% of breast cancers, TNBC's have been shown to be relatively aggressive and display a high risk of metastasis and death within 5 years after diagnosis. TNBC is considered to be vastly heterogeneous and is often used as an umbrella term, encompassing a wide spectrum of entities with marked genetic, transcriptional, histological, and clinical differences. [1]

A rare cancer that is more commonly associated with TNBC, is secretory breast carcinomas- a cancer that occurs due to an over secretion of mucin in the tumor. It is considered a subtype of invasive ductal carcinoma but is prone to metastasis and local recurrence. It is a slow-growing cancer that is best to treat aggressively and it represents less than 0.1% of all cases of invasive breast cancer. More than 90% of secretory breast cancer cases harbor *NTRK3* gene fusions, and are associated with a moderate frequency of additional genomic alterations and a complete absence of either high tumour mutational burden or high tumour microsatellite instability. [2]

To date, there is no clinical consensus on the treatment of secretory breast cancer. As targeted therapies, developed for hormone receptor-positive and HER2-positive breast cancers, are often ineffective against triple-negative breast cancers, possible treatment options often include chemotherapy, radiation and mastectomy. Treatment decisions for secretory breast cancer are made on an individual basis due to the rarity of this subtype of breast cancer. [3]

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[1] Hsiao, Susan J et al. "Detection of Tumor NTRK Gene Fusions to Identify Patients Who May Benefit from Tyrosine Kinase (TRK) Inhibitor Therapy." *The Journal of molecular diagnostics : JMD* vol. 21,4 (2019): 553-571. doi:10.1016/j.jmoldx.2019.03.008

[2] Abstract P2-09-15: NTRK fusions in breast cancer: Clinical, pathologic and genomic findings. Ross et al. https://cancerres.aacrjournals.org/content/78/4_Supplement/P2-09-15.

[3] Li, Lijuan et al. "Clinicopathologic and molecular characteristics of 44 patients with pure secretory breast carcinoma." *Cancer biology & medicine* vol. 16,1 (2019): 139-146. doi:10.20892/j.issn.2095-3941.2018.0035

Current treatment options for metastatic breast cancer are only effective at prolonging progression-free disease, and most cases of advanced disease will progress and symptoms will worsen. It is well known that breast cancers are highly heterogeneous malignancies. Patients with the same clinical stage, histological type and treatment may have diverse outcomes. Molecular differences are considered to be the main reason for this disparity. As a result, genomic testing of breast cancer patients is essential for determining appropriate treatment.

Patients with a diagnosis of metastatic breast cancer understand the limitations of current treatment options, and seek to live their remaining months and years with the best quality of life that they can achieve.

The physical impact of metastatic breast cancer
How the disease presents itself through symptoms, how it progresses, and how it is experienced varies by patient, but many effects of metastatic breast cancer represent a significant or debilitating impact on their quality of life. In our 2012 Metastatic Breast Cancer and Caregiver Survey (2012 survey), patients were asked what impact cancer related symptoms had on their quality of life:

• 54% of patients reported that fatigue resulted in a significant or debilitating impact, and 40% reported some or moderate impact;

• 37% of patients reported that pain resulted in a significant or debilitating impact, and 44% reported some or moderate impact;

These results were further reinforced in our 2017 survey of metastatic patients. A preliminary analysis of the responses of the 21 triple-negative respondents reveals that the key concerns listed by patients in the management of their disease are, managing pain, starting treatment as early as possible following diagnosis, and minimizing/managing the side effects of chemotherapy treatment.

The social impact of metastatic breast cancer
The impact of this disease spreads across all aspects of a patient's life, restricting an individual's employment and career, ability to care for children and dependents, and their ability to socially and meaningfully participate in their community. When asked in CBCN's 2017 Patient Survey (2017 Survey) what kind of impact living with metastatic breast cancer has had on their quality of life:

- 47% of respondents were employed full-time at the time of diagnosis, with only 12% employed full time at the time of the survey;

- 74% of respondents said they had experienced an impact on their mental health as a result of their diagnosis;

- 42% of respondents indicated that their diagnosis had some negative impact on their finances, with 40% reporting a large negative impact on their finances.

The 2012 Survey shared the following in terms of impact on the quality of life of a patient:

• 49% of patients identified significant restrictions and 38% identified some or moderate restrictions to their ability to exercise;

• 42% of patients identified significant restrictions and 42% identified some or moderate restrictions to their ability to pursue hobbies and personal interests;

• 41% of patients identified significant restrictions and 41% identified some or moderate restrictions to their ability to participate in social events and activities;

• 22% of patients identified significant restrictions and 52% identified some or moderate restrictions to their ability to spend time with loved ones.

Other experiences identified by patients: guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of impact of the cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, martial stress/loss of fidelity and affection from partner.

"I'm 43 now and I will be in treatments for the rest of my life. I have a very difficult time still trying to figure out how to move forward while taking advantage of all the wonderful moments I still have. I have no choice but to continue to battle this war that my body has bombarded my family and me with… the most difficult aspect is planning for my mortality and trying to keep my chin up and not burden my family."(Patient 2017 Survey)

4. Experiences With Currently Available Treatments

The goals of current therapy
The goals of current treatment options for metastatic breast cancer include controlling the progression of the disease (extending life), and reducing cancer-related symptoms (extending or stabilising quality of life). Treatment options and effectiveness vary among type of cancer, location of cancer, and how symptoms are experienced.

For secretory breast cancer patients in particular, current treatment options are typically limited to chemotherapy and surgery-typically mastectomy. The use of chemotherapy has been noted to induce a range of side effects, with some patients experiencing minimal effects and others affected by nausea, vomiting and extreme fatigue. Patients treated with chemotherapy often experience significant side effects that interfere with daily activities and impact productivity. There are some indications that secretory breast carcinomas can be resistant to chemotherapy which could leave certain patients with limited options for treatment. Due to the rarity of this disease and the lack of widely researched information available about this condition, it is difficult to ascertain what the standard of care for these patients should be.

In our 2017 Metastatic Breast Cancer Patient survey, the most common site of metastasis was the bone, with 72% of respondents having bone metastases; 35% had liver metastases; 32% had lung metastases; 12% had brain metastases; and 20% had metastasis in other parts of the body.

Key factors for decision-making around treatment:
The respondents in our 2017 survey of metastatic patients indicated that the key factors influencing their decision-making around treatments were as follows:

1. Effectiveness of the treatment-how well the treatment stabilized their disease and delayed progression of their disease.
2. Prolonging life without sacrificing quality of life-being able to maintain productive, active lives with minimal disruption to daily routines.
3. Side effect management-minimizing risk while stabilizing their disease.
4. Cost and accessibility of treatments-affordability and ease of accessing treatments.

Treatment Efficacy:
When asked how important progression free survival was in considering treatments, the metastatic patients in our 2017 survey revealed that efficacy of the treatment is critical to their decision-making. When considering treatment options, respondents indicated that overall survival (88%) and progression free survival of 6 months or more (82%) were the very important considerations when considering treatment options. Progression free survival of 3 to 5 months was very important to 59% of respondents and important to 25% of respondents. Progression free survival of less than 3 months was still very important to 52% of respondents and important to 21% of respondents..

Patients further elaborated on the importance of effectiveness in their decision-making anecdotally:

> *Trying to balance the most effective treatment regime with the least impact on my day to day living / quality of life. Maintaining a certain level of independence is important to me.* (Patient 2017 Survey)
>
> *Effectiveness and ability to spend quality time with my son* (Patient 2017 Survey)

The concept of accessibility of new treatment options also came up numerous times when metastatic respondents in our 2017 survey of metastatic patients were asked about factors that influence decision making. Many indicated that whether or not a treatment was covered provincially could decide what treatment they choose. Every single respondent from the metastatic survey who added additional comments around understanding treatment options expressed concern over whether new treatments would be accessible to them.

Quality of Life:
Quality of life was routinely cited by patients as a key factor in making treatment decisions. In our 2017 survey, quality of life was ranked as a very important consideration by 58% of respondents, and rated as important by 33%.

> *Quality of life is very important to me.* (Patient 2017 Survey)
>
> *Quality of life. Keeping who I am for my daughter.* (Patient 2017 Survey)
>
> *Making sure I have some quality of life so I can spend as much time with my kids and family I don't want them to watch me suffer* (Patient 2017 Survey)

Patient willingness to tolerate treatment side effects
In our 2012 metastatic patient survey, when asked what level of side effects and how much impact on one's quality of life would be worth extending progression-free disease by six months, the message sent by patients was that this assessment can only be determined by an individual patient, in this circumstance.

When asked to rate how much impact different symptoms of cancer and cancer treatment would be considered tolerable:

- Almost two-thirds of patients indicated that when it comes to **fatigue, nausea, depression, problems with concentration, memory loss, diarrhea and insomnia**, some or a moderate impact on one's quality of life would be considered acceptable, and approximately one quarter of patients indicated that a strong or debilitating impact would be considered acceptable. This response was verified by our 2017 survey

results as well, with the majority of respondents indicating that these symptoms were considered acceptable to them.

- 70% of patients indicated that when it comes to **pain,** some or a moderate impact on one's quality of life would be considered acceptable, and 27% of patients indicated that a strong or debilitating impact would be considered acceptable. Again, these results were corroborated in our 2017 survey with the majority of respondents indicating that they were willing to somewhat accept pain as a side effect of their treatment.

Minimal side effects were ranked as an important consideration by 40% of respondents but only ranked as very important by 24% of respondents.

Patient access to local resources and supports during treatment
When living with cancer, many patients experience significant barriers and challenges around availability of health care services and quality childcare in their community. In response to 2012 Survey questions about the availability of supports such as childcare, transportation, and alternative treatments in their community:

- Among patients with children or other dependents, 53% indicated that there is minimal or no access **to appropriate care for their loved ones** when they are experiencing debilitating symptoms related to their cancer, and 40% identified barriers to accessing quality care during cancer treatment.

The financial burden of treating and managing breast cancer
The financial burden associated with living with advanced breast cancer extends far beyond any loss of income during a temporary or permanent absence from employment. In addition to the loss of income during illness, metastatic breast cancer patients can incur substantial costs associated with treatment and disease management.

Research on the financial impact of breast cancer on patients identified the following:

- 80% of breast cancer patients report a financial impact due to their illness.
- 44% of patients have used their savings, and 27% have taken on debt to cover costs.[4]

These findings were consistent with the responses in the 2012 Survey:

- Nearly one third of patients indicated that the **cost of medication, the cost of alternative treatments (i.e. massage, physiotherapy, etc.) to manage symptoms and side effects, and the time required to travel to treatment** had a significant or debilitating impact on their quality of life.
- 24% of patients indicated that the **costs associated with travel** had a significant or debilitating impact on their quality of life, and 41% of patients indicated that it had some or moderate impact on their quality of life.

Patient willingness to tolerate risk
When asked in the 2012 survey about their willingness to tolerate risk with a new treatment:

- 34% were willing to accept serious risk with treatment if it would control the disease
- 45% were willing to accept some risk with treatment
- 21% were very concerned and felt less comfortable with serious risks with treatment

[4] Janet Dunbrack, Breast Cancer: Economic Impact and Labour Force Re-entry. Canadian Breast CancerNetwork, 2010

Need for personal choice
What was revealed in the responses to the open ended questions is that it is imperative that all patients with metastatic breast cancer have access to and the option of taking the drugs. Most patients are well aware of the adverse effects of treatment up front and they want to make a personal choice that works for them.

More treatment options! Few options exist for BRCA negative, TNBC. We need more options and a better prognosis. -2017 Patient

Had you asked me some of these questions four years ago, the answers would have been different. My oncologist tells me that I am running out of treatment options. […] It is very scary to face the day (soon) when I will have no treatment and the cancer will be allowed to run its course. –2012 Patient

I wanted to try immunotherapy, but it is 7500.00 every 3 weeks not covered by private insurance, now will probably have to go on chemo again, and the last ones were very hard on me causing toxicity and having to get blood transfusions -2017 Patient

5. Improved Outcome

Patients living with metastatic breast cancer consider both progression-free survival and overall survival to be important. Progression free survival with a well-tolerated treatment can mean more time spent with a good quality of life, even if the overall survival is similar.

Although CBCN was unable to interview a breast cancer patient who had experience with the treatment under review, we are able to speak to patient's general positions on treatment.

Based on the data from the three multicenter, open-label, single-arm clinical trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431), as well as the recently reported expanded pooled efficacy analysis of 159 patients with TRK fusion-positive cancer treated with Larotrectinib, and a safety analysis of 260 patients who received Larotrectinib regardless of TRK fusion status by Hong et al, patients expect that treatment would deliver clinically meaningful response in their cancer and better quality of life than if they were relegated to chemotherapy alone. Of the five breast cancer patients included in the pooled analysis, 3 experienced a response on Larotrectinib. The pooled analysis also demonstrated that *NTRK* fusion patients had a better prognosis than their non-fusion counterparts in terms of both overall survival (median 44.4 vs 10.7 months) and progression-free survival (median 28.3 vs 1.8 months).

It is important to note that patients are aware that the treatment has been conditionally approved for use in several other global jurisdictions, including by the Food and Drug Administration in the United States, the European Medicines Agency and the National Institute for Health and Care Excellence in the United Kingdom. Since the National Health Service is supporting public reimbursement coverage for the treatment, patients are hopeful for similar coverage in Canada.

Adverse effects
The data from the trial and pooled analysis demonstrated that Larotrectinib was well tolerated; with dose discontinuation occurring in only approximately 2% of patients due to side effects. The most common adverse events were fatigue, nausea, dizziness, vomiting, increased AST, cough, increased ALT, constipation, and diarrhea. Grade 3 and 4 Larotrectinib -related adverse events

were infrequent and dose reduction because of adverse events was only 8% confirming the favorable tolerability profile of the treatment.

Impact of treatment options to patients
By delaying the progression of the disease, this treatment can relieve cancer-related symptoms, and improve a patient's quality of life. Patients living with metastatic and rare breast cancers are looking to be able to access as many options as possible that will delay the progression of their disease and provide them with a good quality of life.

Value to patients
The value to patients of extending the time that their cancer is progression-free cannot be overestimated. Patients living with metastatic breast cancer are aware that their disease will progress with worsening symptoms until death, and embrace opportunities to try new treatments. It is also very important for patients to have quality of life when receiving treatment for their disease. Patients that we speak to on a regular basis acknowledge the importance to have the energy to attend their children's/grandchildren's activities and to spend time with family and friends.

6. Experience With Drug Under Review

Given the rarity of this particular genetic mutation and that this treatment is not widely accessible in Canada, CBCN was unfortunately unable to connect with, and interview, breast cancer patients with experience on the treatment.

7. Companion Diagnostic Test

At this time, NTRK gene fusion testing is only available through a manufacturer-supported clinical testing program and is not implemented routinely in breast cancer care in Canada.

While NTRK gene fusions are rare overall in cancer, and particularly so in breast cancer, accessing testing and treatment is of great importance for NTRK positive breast cancer patients. Recent studies on oncogenomic testing algorithms have indicated that it may be of significant value to test locally advanced/metastatic breast patients who are negative for common oncogenic drivers with an immunohistochemistry screen followed by a confirmatory next-generation sequencing test to ensure that all breast cancer patients who could benefit from this therapy are being identified.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

We note that Larotrectinib, as a tumour agnostic therapeutic, treats cancer patients based on the presence of a specific tumour biomarker rather than the site the cancer originated. As a result, the clinical evidence is based on extremely small sample sizes that may be interpreted as yielding uncertain data. We hope that CADTH will consider continuing to engage the manufacturer and other stakeholders to develop novel approaches to support translation into models of assessment for potential value in clinical practice in Canada.

Funding this type of molecularly targeted therapeutic would provide an important therapeutic option for cancer patients (including breast cancer) whose tumors test positive for an NTRK gene fusion, are metastatic, or where surgical resection is likely to result in severe morbidity, and; have no satisfactory treatment option.

CADTH

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH drug reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   CBCN researched and authored this submission in its entirety.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   CBCN engaged the sponsor of the treatment to access relevant clinical data for this submission.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	x			

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Niya Chari
Position: Director of Public Affairs and Health Policy
Patient Group: Canadian Breast Cancer Network
Date: December 4,2020

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Larotrectinib (Vitrakvi®) for the treatment of adult and pediatric patients with solid tumours harboring NTRK gene fusions 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.**
Name of the Patient Group	**Canadian Cancer Survivor Network (CCSN), and:** • **Advocacy for Canadian Childhood Oncology Research Network (Ac2orn)** • **Colorectal Cancer Resource & Action Network (CCRAN)** • **GIST Sarcoma Life Raft Group Canada (LRGC)**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

The **Canadian Cancer Survivor Network (herein 'CCSN')** led a collective patient input submission on Larotrectinib (Vitrakvi®) to provide a multi-tumor patient perspective on the therapy under review. The following patient advocacy groups thoughtfully collaborated to provide meaningful and compelling patient input:

- **Advocacy for Canadian Childhood Oncology Research Network (herein 'Ac2orn')**
- **Colorectal Cancer Resource & Action Network (herein 'CCRAN')**
- **GIST Sarcoma Life Raft Group Canada (herein 'LRGC')**

All patient groups are registered with CADTH.

Please note: To provide robust and meaningful input, additional tumor type patient perspectives were captured and included in this submission but their respective patient advocacy groups are not represented herein.

Also: While LRGC has contributed to this submission, CCSN was unable to interview a GIST patient who had experience with the therapy under review due to the rarity of NTRK gene fusions in this patient population in Canada and the lack of mutational analysis being performed to inform and drive treatment decisions for GIST across Canada.

2. Information Gathering

To help capture the critically important patient perspective on this tumour agnostic therapy under review, **CCSN** developed a comprehensive and universal patient interview questionnaire that was employed throughout the adult and pediatric patient interviews as highlighted below. On **September 13, 2020**, CCSN reached out to the **LOXO 101 clinical trial** principal investigator at MD Anderson, **Dr. David Hong,** overseeing the study, to help identify patients who would be willing to provide their experience with Larotrectinib by participating in a telephone interview. On **September 22nd, 2020**, CCSN also reached out to an online colorectal cancer support group in the U.S. and Canada (**Colon Town**) respectfully requesting patients contact us if interested in providing their

experience with the therapy under review. Additionally, the newly formed online **NTRKers Support Group** was contacted on **September 24th, 2020** to request assistance with patient accrual for telephone interviews capturing their experience with the therapy. CCSN was also able to secure Canadian patient perspectives through **Canadian Clinicians** who have been prescribing the therapeutic through Bayer's FastTRK Program and managing these patients in Canada. CCSN enlisted the assistance of Ac2orn who provided pediatric patients with experience with Vitrakvi. Telephone interviews with **adult patients** took place between **October 21, 2020 and November 16, 2020**, while pediatric patient interviews spanned between **October 15, 2020 and October 30, 2020**, with an additional interview having been conducted in **February 2019**. CCSN spoke directly to **8 adult patients** who provided first hand, compelling, relevant and high quality telephone interviews whose tumor type distribution is as follows:

- 3 Thyroid Cancer Patients (**Patients A, D & H**)
- 2 Lung Cancer Patients (**Patients B & G**)
- 1 Salivary Gland Patient (**Patient C**)
- 1 Colorectal Cancer Patient (**Patient E**)
- 1 Glioblastoma Multiform (GBM) Patient (**Patient F**)

AC2ORN kindly provided CCSN with interview data for **4 pediatric patients** whose tumor type distribution is as follows:

- 3 Thyroid Cancer Patients (**Patients J, K & L**)
- 1 Infantile Fibrosarcoma (**Patient I**)

In total, CCSN has captured the valuable patient perspectives representative of ***6 different cancer disease sites***. The qualitative data from the patient interviews is summarized and represented entirely in the attached **APPENDIX** [containing both the adult (**TABLE 1**) and pediatric (**TALBE 2**) data] and will serve as the basis for this qualitative submission.

3. Disease Experience

Adult patients who were interviewed were asked if they had any cancer-induced symptoms before starting Larotrectinib with which they struggled. Seven out of eight adult patients reported debilitating or challenging cancer-induced symptoms which significantly compromised their quality of life. The symptoms included: pain, fatigue, poor appetite, shortness of breath, wheezing, and coughing up blood. **Patient E** (colorectal cancer) reported having to endure a rather large chest wall mass that had surfaced under her left breast and was a constant source of odor and seepage – it prevented her from wearing undergarments and regular clothing as well as leaving her home for any reason other than medical appointments.

"Yes, that terrible thing under my left breast – it was gross and growing, and oozing, and it was so stinky. It was so hard to control. I had to change the bandages all the time throughout the day."

Patient H (thyroid) experienced dreadful shortness of breath due to her thyroid cancer which made it impossible for her to climb her stairs in her home or walk her dog up the hill in her neighborhood. **Patient A** (thyroid) wheezed all the time and was no longer able to exert herself. Walking became problematic. **Patient B** (lung cancer) experienced painful hips and poor appetite and **Patient D** (thyroid cancer) had multiple cancer induced symptoms due to metastatic disease in the lungs which made it difficult for her to breathe, and as a result move around. These symptoms ultimately compromised the patient's quality of life, reducing daily activity and function. Please see **TABLE 1** appearing in the attached **APPENDIX**

Pediatric patients experienced the following cancer-induced symptoms: trouble swallowing and breathing (**Patient J:** Thyroid), difficulty breathing, loss of appetite and cachexia (**Patient K**: Thyroid). **Patient I** (Infantile fibrosarcoma) experienced none and no reply was captured for **Patient L** (Thyroid).

4. Experiences With Currently Available Treatments

The 8 interviewed adult patients accessed currently available therapies for the treatment of their respective cancers. **Patient A** (Thyroid) accessed thyroidectomy, radioactive iodine, stereotactic beam radiation for her T2 cervical spine tumour, and 4 surgical procedures to her neck which included the previously stated thyroidectomy and 3 neck dissections. The treatments did not control her cancer because she continued to experience disease progression. And she endured ghastly treatment-induced side effects:

"Surgical procedures were simple but painful….the beam radiation therapies were the worst. To prepare, they had to put a needle through my face and that was awful! They had to make a mask for me to undergo an MRI for the therapy. It gave me huge stress and diminished my quality of life. I am now always freaked out when I do an MRI. I had a horrible sore throat over the therapy. I lived on chocolate milk for days because of it. So painful!! I also had to sleep on multiple pillows after that because I couldn't sleep flat. And the same after my surgeries. Horrible quality of life. Therapies also put me into early menopause which was so horrible for me at such an early age."

The other two Thyroid Cancer patients (**Patient D and H**) had similar treatments: thyroidectomy followed by radioactive iodine, external beam radiation, more radioactive iodine, more surgery, gamma knife, and endocrine therapy (Synthroid). Again, treatment-induced side effects were quite unbearable, particularly, in respect of the radiation which produced painful sore throats resulting in an inability to drink, eat or swallow and the disease was not controlled.

"*My quality of life was oh so very unpleasant. It may have been short term yes, but there were months of leading up to RAI, scans, bloodwork, bone scans, isolated, feeling nauseated and they kept telling me to not throw up or you will be back in here. I found it difficult to swallow and eat or drink. My salivary glands blew up. It was horrible."*

The two Non-Small Cell Lung cancer patients (**Patients B and G**) underwent the following treatments to try to manage their disease:

Patient B endured external bream radiation for painful metastatic disease to the hips, cyberknife for a metastatic lesion to the brain, cisplatin + gemcitabine, pemetrexed, Pembrolizumab, docetaxel. The only therapy which allowed for tumour shrinkage was the pemetrexed but it, along with the others (save the Pembrolizumab) induced significant side effects. The patient felt quite ill most of the time and could not function. The cyberknife compromised his short term memory resulting in a permanent suspension of his driver's license.
Patient G underwent toxic chemotherapy followed by radiation, Opdivo, and more chemotherapy. The patient never achieved any tumour shrinkage on any of the treatments and side effects were quite pronounced, diminishing his quality of life throughout the entire time he was on therapy.
The Salivary Gland patient (**Patient C**) underwent high dose radiation targeting the face, head and neck and upper chest. He also underwent multiple surgeries, and more radiation, none of which were successful in controlling his cancer, for his cancer continued to proliferate and propagate. He experienced fatigue, loss of appetite, skin issues, burning, lost half his beard, speech impediment (which is problematic for an attorney at law), radiation and surgery-induced chronic pain requiring pain medication (opiates).
Patient E (colorectal cancer) accessed FOLFOX, followed by Pembrolizumab, radiation therapy to her brain, followed by Pembrolizumab + FOLFIRI. Her quality of life was quite good on the Pembrolizumab but progressed nevertheless on that therapy. She experienced countless side effects on the chemotherapies. In her words, she was "***sickly and shaky all the time. I would feel faint and oh so awful all the time."***

Patient F (GBM) had debulking surgery followed by Temozolomide and radiation. He also had adjunctive therapy (hyperthermia), with the assistance of a naturopathic doctor. The goal of the adjunctive therapy was to increase the efficacy of the radiation. According to the patient, his surgical experts claimed the resection was successful but cautioned that a GBM diagnosis would inevitably recur and was waiting to resurface. The patient had a horrific reaction to the chemotherapy regimen: weakness, fatigue, and direct recall had been compromised.

Pediatric Patients J, K and L were diagnosed with **thyroid cancer** and accessed standard of care therapies for the management of their disease. Patients underwent invasive surgeries (thyroidectomies) which caused long term complications and required a significant amount of recovery time. Radioactive iodine (RAI) was also administered, which isolated the child from the family, and took an enormous toll both physically and emotionally on the child, whose ability to rationalize what was happening to him/her was well beyond the scope of their understanding. None of these therapies were effective in controlling these patients' cancers. The child's cancer continued to progress. Interviewed families expressed the challenges associated with having undergone conventional therapies, including short and long-term side effects: change in taste buds, hypocalcaemia, weight gain/loss, and nausea.

Patient I (**Infantile fibrosarcoma**) underwent toxic chemotherapies which included vincristine + actinomycin followed by ifosfamide, and doxorubicin + ifosfamide. While there was some initial reduction in tumour size, the tumour eventually grew during the first two regimens. The patient suffered excruciating eczema on all three chemotherapy protocols, to the point where her skin would flaked off. Her sleep was disturbed repeatedly, experienced weight loss, food allergies, edema, and a failure to thrive. Physical milestones were not being met until chemotherapy ceased.

"She was physically weak and could not crawl or walk or meet other physical milestones until chemotherapy ceased. She was regularly an in patient in hospital due to infections and nutritional issues. We spent weeks on end in hospital which seriously affected her quality of life and her ability to develop."

As for GIST patients: the preferred initial treatment is surgical removal of the tumour, where possible, often followed by adjuvant treatment with the first-line medication, imatinib. If surgery is not possible, or in the case of metastasis, the current algorithm for treatment involves a series of oral medications: imatinib, sunitinib, regorafenib, and the new drugs ripretinib and avapritinib. The efficacy of each of these medications depends entirely on identifying the driver mutation(s) of the patient's tumour. Currently, mutational analysis is not yet deemed a standard of care for GIST across Canada. However, when treatment is guided by the mutational status of a patient's tumour, the disease can typically be very well managed medically, and for many years, with limited, manageable side effects. However, some less common GIST driver mutations respond very poorly, or not at all, to the current standard therapies and the disease progresses unchecked. ***This is the case for GIST patients where the tumour is driven by an NTRK gene fusion.***

5. Improved Outcomes

All interviewed adult patients provided their perspective on the improvements they would wish to see associated with new therapies – improvements that are currently not available with standard of care therapies, especially in respect of cytotoxic therapies. Adult patients expressed the following: a desire to access a therapy that would promote good quality of life while effectively controlling their disease (through either disease stability or disease regression). According to the data captured in **TABLE 1** of the attached **APPENDIX,** patients would wish to see improvements in:

- survival, if not a cure altogether,
- cancer-induced symptom control,
- the drug's toxicity profile, inducing no or minimal side effects, and
- ease in the drug's administration, through a capsule or oral solution formulation at home.

According to all 8 interviewed respondents, accessing a therapy that can prolong life, or can provide a highly sought-after cure, with minimal side effects that promotes quality of life and is easily administered in the comfort of their homes, would significantly ameliorate their lives. It would permit them to resume normal activities, be gainfully employed, spend time with their friends and family (especially their cherished grandchildren) and would permit them the freedom to "***go back to their old life but with a greater appreciation for what they have been through***." Furthermore, 7 of the 8 adult patients maintained that Larotrectinib currently possesses these desired improvements and were grateful to have been able to access this remarkable therapy. **Patient B** (Non Small Cell Lung Cancer) and **Patient C** (Salivary Gland Cancer) provided the following quotes respectively:

"I believe it has helped me with quality of life and stopping my cancer from growing. I do not go to the doctor every week. I take an oral therapy which is great. I get to do more things with family and friends. If I had started it earlier and avoided the other toxic therapies, this would have been ideal for me!!"

"Vitrakvi is what gave me this idea to answer your question. It has done more than save my life. It made me feel good again. It has gone beyond what most people experience and would expect from a cancer therapy. All cancer therapies should aspire to this."

These were sentiments that essentially echoed the feedback of the balance of the adult patients across the multiple tumour histologies.

Pediatric patients who undergo therapies for the treatment of their cancers, will experience significant treatment-induced side effects which will inevitably compromise the patient's quality of life, ability to thrive, ability to participate in family functions and social events. Families who were interviewed for this submission reported the following treatment-induced toxicities:

- **Patient I** was a **3 year old female** who was diagnosed with **infantile fibrosarcoma** who experienced severe eczema, insomnia, weight loss, multiple food allergies, critically elevated albumin levels, edema, failure to thrive, physical weakness, inability to reach physical milestones, multiple infections and poor quality of life due to countless hospital stays.
- **Patient J** was a **9 year old male** who was diagnosed with **thyroid cancer** and suffered hypocalcaemia and hypothyroidism.
- **Patient K** was a **4 year old male** who was diagnosed with **thyroid cancer** and having had a thyroidectomy and open heart surgery, the recovery period was extensive and gruelling for this little boy. It was followed by 2

RAIs which imposed a number of restrictions on the child, proving challenging and emotionally straining on the patient and family.

- **Patient L** was a **12 year old male** who was diagnosed with thyroid cancer and having had 2 surgeries and 2 RAIs, he experienced weight gain and depression from the multitude of therapy-induced side effects.

Families with children whose tumours harbor NTRK gene fusions would like their children to access treatments that do not induce long term side effects such as mobility challenges, sight changes, growth/endocrine issues, secondary cancers or other challenging side effects as noted above. The short term side effects of standard of care therapies for pediatric patient cancers may be tolerable, provided they are manageable. However, the long term side effects are not acceptable and, therefore, require a new therapeutic that may provide a lifeline by way of not only prolonged survival but improved drug-induced toxicities for this patient population. Interviewed families maintain **Larotrectinib** to be such a therapy because it has been easy to use, provided improved QoL, with few side effects. One parent reports:

"Unlike the chemotherapy treatments we experienced, this drug has enabled her (and consequently the family) to lead a relatively normal life, whilst controlling her disease very effectively. This has been revolutionary for us."

In the words of one very grateful parent:

"***We cannot stress enough how grateful we are for this treatment, for my daughter especially, but also for the rest of our family who endured months of grueling chemotherapy regimens which were ultimately ineffective in dealing with the cancer. We hope that families around the world can have the experience of accessing this drug without having to meet drug trial requirements and without first having to try conventional chemotherapy treatments. The speed with which Larotrectinib deals with the cancer and minimal nature of the side effects we have observed are astounding."***

6. Experience With Drug Under Review

The attached **APPENDIX** contains **TABLE 1** and **2** which include the demographics and treatment-related experiences for **8 adult patients** and **4 pediatric patients**, respectively, currently undergoing the therapy under review. Three Adult Patients accessed the therapy through the **LOXO 101** study in the U.S., four adult patients accessed the drug through Bayer's Patient Support Program in Canada, and one adult patient accessed the therapy through Health Canada's Compassionate Use, *after learning they all tested positive for the unique biomarker, the NTRK gene fusion.* Patients accessed the therapy with great anticipation for they had all exhausted standard of care therapies and were unable to continue to manage their advancing disease. **Patient C** (Salivary Gland Caner) and **Patient H** (Thyroid Cancer) commented:

"I never really had a good response to any of the previous therapies. My tumours just kept growing and spreading which is why I am so happy to be on Vitrakvi. I became so ill where I was given a timeline for death."

"Nothing worked for me. My disease progressed on every therapy I have been on before Larotrectinib."

One patient experienced no side effects whatsoever while on the therapy. The balance of patients experienced side effects which included: withdrawal symptoms as they approached their next dose, nerve sensations, skin tenderness, ear pain, minor/moderate fatigue, minor cough, general unwellness which resolved with a dose adjustment, and elevated liver enzymes (AST and ALT). **Patient F** (GBM) was quite emphatic and insisted the author of this submission include the following:

"Oh, and by the way, the muscles on the side of my face are sore from smiling so much cuz I'm on Larotrectinib!"

Patients considered these side effects to be quite tolerable and relatively minor in comparison to previously accessed therapies and rated their quality of life (QoL) with high scores of either 8, 9 or 10 (save Patient G who rated his QoL with a score of 6). According to **ALL adult patients however,**, this tumour agnostic therapy has delivered a clinically meaningful response. Their cancer has either **resolved completely (3)** or **responded significantly (5)** providing them with a semblance of a normal life. **Patient B** (Non Small Cell Lung Cancer) reports:

"I had the most extraordinary response. I had so many tumours – they couldn't count how many tumours I had in my lymph nodes, liver, kidneys etc. and they certainly couldn't remove them surgically. I remember, at one point, they had doubled in size and number in just 5 days. They were growing and spreading so fast. I recall being so ill in hospital bed just before starting this Vitrakvi. I was told I had 3-4 weeks to live. I couldn't even sit in a chair. They started me on the drug and in just one week, I felt remarkably better and I kept feeling better and better after that. After the first CT scan, all my tumours were gone except for one which had shrunk by 65%. Now that tumour has disappeared and is merely scar tissue. I no longer have any sign of cancer detectable through CT and there have been no new tumours. I am an NED patient because of Vitrakvi. I am fully restored."

Seven of the eight patients struggled with cancer induced symptoms prior to starting Larotrectinib and in each case the therapy provided significant resolution of those symptoms. **Patient H** (Thyroid) reports: "***Definitely. My shortness of breath has resolved. Now I can walk the dog up that hill and do the stairs in my home."***

No patient experienced a treatment interruption due to Larotrectinib-induced toxicity and efficacy was radiographically confirmed in each patient through either CT or MRI. Patients repeatedly expressed their appreciation to be accessing an easily administered oral therapy (capsule or liquid formulation) that can be taken in the comfort of their homes, sparing them countless visits to cancer centres that would ultimately incur travel expenses and precious time away from home and family. All interviewed patients expressed profound regret and disappointment with having accessed previous therapies that failed to successfully treat their cancers which caused each indescribable pain, suffering and anguish. Had their tumours been identified to harbor the NTRK gene fusion, once again they could have been spared painful surgeries, radiation therapies and countless cycles of chemotherapy whose long term side effects could have been avoided. **Patient B** (Lung Cancer) comments: ***"I wish I could have been spared dizziness, short term memory loss and so much more from the other therapies I had to endure. This is a therapy that spares patients from toxic effects. I have had to give up driving because of brain radiation affecting cognitive skills and memory loss. I just didn't want to kill someone or myself. This could have been avoided had I been able to access Vitrakvi. Others can be spared this."***

And **Patient C** (Salivary Gland) adds:

"***Look at what I am able to produce in life because of Vitrakvi. Instead of being in a hospital bed, I am cycling, running and arguing cases in front of juries and feeling so very healthy and doing it with so much zest. Even if I had survived on other chemos, I would be doing it with so much fatigue and toxicity, it would not be the same. I get to go out and enjoy life at restaurants, theatres, I travel….and I enjoy the company of my family and friends. I genuinely contribute to life."***

All interviewed patients believe the therapy has been and continues to be their lifeline, a "miracle" drug without which they would not be alive today. They credit their survival and ability to function at an almost normal level entirely to Larotrectinib. **Patient F** (GBM) who is a single father of 3 maintains:

"***Absolutely. Without a doubt. Because without it, I would likely not be here today. Without it, there is no hope for me or my 3 children. They would not have a parent."***

TABLE 2 in the **APPENDIX** captured pediatric patient data, including the patient's experience with the therapy under review. All 4 pediatric patients had access to the therapy through a clinical trial. According to the data, compared to previously administered therapies, such as chemotherapies (actinomycin, ifosfamide, and doxorubicin), surgeries (thyroidectomy), radiation therapy (radioactive iodine), Larotrectinib is a highly tolerable therapeutic, effective at reducing the bulk of disease, has a low side effect profile and allows for excellent quality of life. Larotrectinib has a superior toxicity profile when compared to cytotoxic drugs and is easily administered as an oral therapy at home in liquid formulation. Patients are resuming their normal life without fear of risk from infection due to therapy-induced neutropenia. All 4 pediatric patients have had a remarkable response to Larotrectinib, without which these children would likely not be with their families today. This tumour agnostic therapy has saved the lives of all 4 children, achieving disease response rates that have seldom been observed in traditional therapies for the management of Infantile Fibrosarcoma and Pediatric Thyroid Cancer. Patients' families cited the following treatment-induced side effects which were purported to be mild in comparison to previously accessed therapies: slight dizziness, muscle soreness, weakness, elevated liver enzymes, weight gain, and withdrawal-like symptoms. As a result of accessing Larotrectinib, the patient's disease has either resolved completely or significantly and allowed the children to resume a level of normalcy their parents could only dare to dream of with sadness in their hearts. For those patients who experienced cancer-induced symptoms prior to starting Larotrectinib, all reported a significant improvement in those symptoms after starting the therapy and no patient was required to stop the therapy due to a treatment-induced toxicity. Response to Larotrectinib was confirmed through either x-ray or CT and those findings were received with great elation. As an example of what Larotrectinib has been able to achieve, we cite the case of **Patient K**. At the age of 5 years, a scared little boy (**Patient K – Thyroid Cancer**) undergoes a thyroidectomy for the treatment of his thyroid cancer and then radioactive iodine (RAI) which required not only isolation while in hospital as an in-patient but isolation from his family due to his mother having just given birth to his baby brother. The little boy was required to go home to his grandparents to continue to the isolation period. This frightened little boy, who is not only recovering from invasive surgery and a toxic therapy is not quite certain why he cannot be comforted by his mother, while feeling vulnerable and quite ill. Due to cancer progression, he continues to undergo additional RAIs which prove ineffective at controlling his disease. Due to cancer progression, he became quite ill and was faring poorly. After testing positive for the NTRK gene fusion, **Patient K** had a remarkable response to Larotrectinib and put his cancer into remission. Currently, as a sixth grader, he is thriving and meeting milestones. What a gift both the patient and family received from this life-altering therapy. All patients' families wish they could have been provided with the opportunity to have determined their child's mutational status at diagnosis so they could have spared their child the agony of unnecessary, painful and toxic treatments. Had they undergone genomic profiling that would have identified their child's tumour mutational status, they would have accessed a highly targeted, less

toxic, easily administered and highly effective therapeutic capable of achieving a high quality of life and durable response for their child. They wish this not only for their child but for other pediatric patients going through the journey as well.

7. Companion Diagnostic Test

All interviewed patients, both adult and pediatric, confirmed they tested positive for the unique biomarker, the NTRK gene fusion, which allowed them to access the therapy under review. Two U.S.-based patients were tested at [redacted] and another U.S.-based patient was tested at [redacted]. Their TRK positive cancers rendered them candidates for the LOXO 101 clinical trial. **Patient B's** cancer was sent from [redacted] to Boston Massachusetts, **Patient E**'s cancer was tested through Bayer's FastTRK Program, **Patient F**'s cancer was tested at [redacted] **Patient G's** cancer was tested at [redacted] and **Patient H's** cancer was sent from B.C. to Boston to be tested through Foundation One. Two of the eight patients were required to travel to have their tumours tested for the NTRK gene fusion – both of whom were U.S. based patients (**Patient A and Patient D**) and one of the eight Canadian patients (**Patient F - GBM**) was required to pay out of pocket for the testing ($8200 CDN – Foundation One). While this was a considerable expense incurred according to the Canadian patient, he claims it was well worth it knowing that a therapy became available to him due to the identification of this novel biomarker. Additionally, based on his cancer's complete response to the therapy, it was unequivocally the best investment he has ever made. For the balance of the patients whose testing was covered, the cost was assumed by either the trial, insurance, or Bayer's FastTRK Program. The test that was readily accessed by adult patients to identify NTRK gene fusions was **Next Generation Sequencing**. Four of the eight adult patients waited a considerable amount of time (2-5 months) for the test results to be generated, citing constant stress and anxiety in anticipation of those results being generated. **Patient A** (Thyroid Cancer) comments:

"***It was very stressful. I worried that I had stuff growing in my body and I wasn't receiving any treatment. I had lots of anxiety. I couldn't wait to receive those results to see if there was something I could access."***

The balance of the adult patients waited 2-4 weeks to have their test results generated. All adult patients were extremely grateful to have accessed testing for it allowed them to qualify and experience a lifesaving or, at the very least, a life prolonging therapy based on the identification of a unique biomarker. This clearly underscores the need to conduct upfront testing in the metastatic cancer population. While TRK positive cancers may be rare across multiple tumor types, testing to identify the patients who qualify for this tumour agnostic therapy will ultimately change the treatment paradigm and guide treatment decisions which will indeed be life altering for patients and their families. The result according to the attached **APPENDIX** is improved patient outcomes. This tumour agnostic therapy clearly delivers on the promise of precision medicine guiding treatment, where tumour genetics rather than tumour site of origin define the treatment approach. This biomarker treatment approach was also evident with the pediatric patients interviewed whose outcomes were also significant improved due to Larotrectinib. All **four pediatric patients** had exhausted standard of care therapies and given no hope for additional treatment options. However, tumour samples were sent for testing and revealed all four patients were candidates for Larotrectinib due to the identification of an NTRK gene fusion. These pediatric patients (**Patients I, J, K and L**) responded in the most remarkable fashion to the therapy and have continued to respond, allowing them to resume an active, full and joy-filled life. Their families are eternally indebted to what they refer to is a "*miracle drug*". Aside from one patient (**Patient J**), no patient had to travel to access testing, and no patient was required to pay out of pocket for the test, nor did families of the pediatric patients wait extensive periods of time for test results to be generated. One parent gratefully expresses:

"Larotrectinib literally saved my son's life. We were completely out of options and had to move heaven and earth to find a doctor who might be able to help. When he started on this trial, and it worked, after years of disappointment, it felt like a miracle. Access to this medication is absolutely essential for kids who have NTRK positive tumours. It is my belief that this could be extremely helpful as a first lien treatment even before surgery in some cases."

8. Anything Else?

The **12 interviewed patients** provided thoughtful and compelling examples of why Larotrectinib was worth accessing. Their values and preferences were captured in the attached **APPENDIX** but we would like to highlight some of the remarkable benefits experience by patients: **Patient A** is able to spend time with friends and family (time she would not have otherwise been afforded), with excellent QoL, is a contributing member of her community as she interacts on a daily basis due to increased wellbeing. **Patient B** was able to celebrate his 60th birthday with a large attendance from those who care deeply for him, saw the birth of his grandson whom he

adores and with whom he spends a great deal of time. Additionally, he was able to attend his daughter's convocation and assist his son with the purchase of his first home. **Patient C** is able to cycle, run, argue cases in front of a jury, enjoys life with zest, dines at restaurants, attends theatres, travels, enjoys his family and friends and genuinely contributes to life in a meaningful way. **Patient D** celebrates every day by doing normal things which, according to her, is so extraordinary. As she puts it: "***There is extraordinary in the ordinary***". **Patient E** enjoys her life by spending time with her precious grandchildren and children. Her grandchildren are extremely active and it's entirely due to the therapy that she is able to keep pace with them. They bring her joy and fulfillment every day of her life. **Patient F** – a GBM patient - is alive and NED today because of the therapy. He has created a YouTube channel for GBM patients interested in learning more about Larotrectinib and has also been able to parent his 3 children as a single father, which according to him, is the greatest privilege of all. Central Nervous System tumours are quite aggressive yet Larotrectinib has achieved not only disease control in this patient, but complete remission of disease over a prolonged period of time for which both the patient and his children are immensely thankful. **Patient G** has been afforded the luxury of spending time with his wife and children, time he claims he would not have otherwise had. He claims he has been given a precious gift. **Patient H** became quite emotional in citing what she has been able to accomplish or fulfill. She claims it has provided her time with all those she loves deeply and allowed her to live longer. Larotrectinib has given her the gift of hope every day. All four pediatric patients (**Patients I, J, K and L**) have similar stories. They lead a life which is comparable to their peers. They are thriving, adored by their siblings, socially engaged, feeling quite healthy, playful, reaching milestones, and brought their cancer into a no evidence of disease status for years and except for the occasional mild side effect, feeling quite well. The use of Larotrectinib, in both our adult and pediatric patients, resulted in improved outcomes. It supports the use of a biomarker guiding the delivery of a targeted cancer therapy. This targeted therapy, agnostic to a tumor's tissue of origin, clearly highlights the era of precision medicine we now find ourselves in that is guiding the treatment of metastatic cancer in Canada. Of noteworthy importance is the fact that ***no other therapy previously accessed by any interviewed patient was capable of delivering a durable, sustainable or lasting response when compared to Larotrectinib***. In the 12 interviewed patients, **Larotrectinib delivered the most robust and durable response, compared to previously accessed therapies (such as chemotherapies, immunotherapies, radiation therapies, and surgeries),** with a favorable toxicity profile in both our pediatric and adult patients diagnosed with TRK fusion cancers. And all patients continue to show durable responses. To deny patients, including very young pediatric cancer patients, access to this highly effective drug would be a shame. All interviewed patients had failed previous treatments for their tumour type including surgery, radiation and systemic treatments like chemotherapy and immunotherapy. But Larotrectinib demonstrated a level of benefit unlike any other previously accessed treatment in these patients and to also observe a remarkable benefit in pediatric TRK fusion cancers is also quite noteworthy for there are relatively few treatment options available for these childhood cancers, such as Infantile Fibrosarcoma and pediatric thyroid cancers. It is encouraging and gratifying to see the consistency in Larotrectinib's durability and response rates across multiple tumour types and ages, which merely confirms the value in testing patients for genomic alterations, like NTRK gene fusions. To have observed the magnitude of responses in our interviewed patients who had either progressed following prior treatments or who had no remaining acceptable alternative treatments confirms that Larotrectinib is effective and amenable for long term administration. In BRAF Wild Type/MSI-High or MMR-D colorectal cancers, it can achieve antitumor activity after multiple lines of therapy provided an NTRK gene fusion is identified, as per our interviewed patient. Furthermore, the therapy had a pronounced and durable antitumor activity in all our interviewed patients [thyroid, NSCLC, Salivary, GBM, (potentially GIST), pediatric thyroid, Infantile Fibrosarcoma] regardless of patient age or tumour type because their cancers had been identified to harbor TRK fusions which predict response to Larotrectinib. If publicly funded, Larotrectinib would be an extremely important therapeutic option for cancer patients whose tumours test positive for an NTRK gene fusion, are metastatic, where surgical resection is unlikely, or have progressed following treatment. 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. We, therefore, strongly support and urge that a positive funding recommendation be issued for Larotrectinib for the treatment of NTRK gene fusion positive tumours. We believe Larotrectinib aligns well with the identified patient need for a new, effective, easily administered treatment option that is capable of maintaining a high quality of life while targeting tumours based on the presence of a specific biomarker.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

CCSN commissioned the services of Filomena Servidio-Italiano (Blue Ribbon Project) to author this submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

CCSN commissioned the services of Blue Ribbon Project to oversee the coordination of this collective patient input submission.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Jackie Manthorne
Position: President & CEO
Patient Group: Canadian Cancer Survivor Network (CCSN)
Date: November 27, 2020

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer			X	
Taiho			X	
Amgen			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Filomena Servidio-Italiano
Position: President & CEO
Patient Group: Colorectal Cancer Resource & Action Network (CCRAN)
Date: November 25, 2020

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

We are being assisted by Filomena Servidio-Italiano who is preparing the joint submission on behalf of CCSN.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer	X			
Blueprint Medicines		X		
Novartis Canada			X	
Pfizer Canada			X	
Remsoft	X			

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: David Josephy
Position: President
Patient Group: GIST Sarcoma Life Raft Group Canada
Date: November 24, 2020

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

The pediatric cancer patient and family interviews for this submission were conducted by Ac2orn without any outside help.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

The pediatric cancer patient and family interviews for this submission were conducted by Ac2orn without any outside help in terms of the collection or analysis of the data.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Antonia Palmer
Position: Co-Founder
Patient Group: Advocacy for Canadian Childhood Oncology Research Network (Ac2orn)
Date: November 26, 2020

APPENDIX

TABLE 1: LAROTRECTINIB RESUBMISSION: ADULT PATIENT INTERVIEW HIGHLIGHTS

INTERVIEW QUESTION	PATIENT A	PATIENT B	PATIENT C	PATIENT D	PATIENT E	PATIENT F	PATIENT G	PATIENT H
PART A: DEMOGRAPHICS/INFORMATION GATHERING								
1. INTERVIEW DATE, TIME & METHOD	October 21, 2020 10:00-11:45 a.m. Telephone	October 21, 2020 1:00-3:00 p.m. Telephone	October 21, 2020 4:00 – 5:30 p.m. Telephone	October 22/20 2:00-3:10 p.m. Telephone	October 27, 2020 2:00 – 4:00 p.m. Telephone	October 30/20 3:00 – 4:30 pm Telephone	Nov. 2, 2020 10:00-11:20 am Telephone	Nov.16, 2020 11:00 -12:30 p.m. Telephone
2. PATIENT'S AGE OF DIAGNOSIS, CURRENT AGE AND GENDER (M, F, NON-BINARY)	- 28 years old - 53 years old - Female	- 54 years old - 61 years old - Male	- 57 years old - 63 years old - Male	- 32 years old - 49 years old - Female	- 51 years old - 55 years old - Female	- 48 years old - 50 years old - Male	- 63 years old - 66 years old - Male	- 34 years old - 56 years old - Female
3. CITY & PROVINCE/STATE	Allentown, Pennsylvania, USA	Burlington, Ontario Canada	Oklahoma City, Oklahoma U.S.A.	Opelousas, Louisiana USA	Toronto, Ontario Canada	Langley, B.C. Canada	St. Bruno de Montarville, Quebec	Lake Country, BC Canada
4. A. MARITAL STATUS (S/M/D)	A. Single	Married	Married	Married	Widow	Divorced, Single Dad	Married	Married
B. CHILDREN?	B. No	2 Children, Ages: 29 and 30	No	No	3 Male Children (36, 34, 31 years) and 4 grandchildren	3 Children, (21 yr daughter, 17 yr son, 15 yr daughter)	1 Son (42 years old) One grandson	27-year-old son and 22-year-old daughter
5. OUTREACH METHOD? - MD ANDERSON CLINICAL TRIAL - NTRKers ONLINE SUPPORT GROUP - CANADIAN CLINICIAN (FASTTRK) - OTHER?	NTRKers Website	Canadian Clinician	M.D. Anderson Clinical Trial	MD Anderson Clinical Trial	Canadian Clinician	Canadian Clinician	Canadian Clinician	Canadian Clinician at BC Cancer Agency
6. TREATMENT CENTRE	[redacted]	[redacted] for Brain Mets: [redacted] for rest of treatments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PART B: DISEASE EXPERIENCE & EXPERIENCE WITH CURRENTLY AVAILABLE THERAPIES								
7. A. TYPE OF PRIMARY CANCER?	A. Thyroid, Follicular/Papillary variant	Non-Small Cell Lung Cancer (NSCLC)	Salivary Gland Cancer	Papillary Thyroid Cancer	Colorectal Cancer (adenocarcinoma)	Glioblastoma Multiform (GBM)	Non-Small Cell Lung Cancer (NSCLC)	Papillary Thyroid Cancer
B. DATE OF FIRST DIAGNOSIS?	B. September 2004	November 20, 2013	October 2014	September 3, 2003	February 6, 2016	October 24, 2018	August 2017	June 1998
C. DATE OF METASTATIC DIAGNOSIS	C. September 2008	November 20, 2013	Summer 2016	July 2005	"Approximately one year later. I can't really remember. I am a bit fuzzy on this."	N/A	August 2017	January 2017
8. A THERAPIES RECEIVED BEFORE LAROTRECTINIB (VITRAKVI)? B. DID THOSE TREATMENTS CONTROL YOUR CANCER? Y/ N (PLEASE EXPLAIN)	A. - "I had 4 doses radioactive iodine and stereotactic beam radiation for my T2 cervical spine tumour. - I also had 4 surgical procedures to my neck which include thyroidectomy and 3 neck dissections - then I had Zometa infusions for my bones."	"Didn't necessarily do treatments immediately because they had to inspect the 1.5 L pleural effusion in my lungs. I did radiation to deal with the pain in my hips and lower vertebrae at Christmas 2013. In Jan.2014 I went to [redacted] to do a brain MRI and later went to an oncologist to deal	"I had a high dose radiation (6 weeks daily) targeted to my face, head and neck and upper chest as well as surgery throughout couple of years. - In Oct 2014 I was diagnosed with a lump in my cheek. - So in Nov 2014 I had surgery.	"- In Sept 2003: I had a Thyroidectomy. - In Dec 2003: Radioactive Iodine. - Jan 2004: I had 7 weeks of external beam radiation to my neck. -Dec 2004: I had my 2nd radioactive iodine. - In Sept 2018: I had Surgery	"I received brain surgery. Then I got Folfox but I was so sick on this treatment – so very sick. I then received Keytruda and my life changed for the better. It saved my life. Then I had brain radiation. Then I had folfiri and Keytruda."	"I had debulking surgery for my GBM on October 31, 2018. Then I had Temozolomide (chemo) starting December 4, 2018 till January 8, 2019 along with some radiation (60 grays) but I had to stop the chemo because my platelets were so very low. They had gone down to	"In August 2017, I received chemotherapy and radiation. Then I received immunotherapy (Opdivo). Then I received more chemotherapy. My treatments ended in early 2019."	"In June 1998, I had surgical resection of the right lobe of my thyroid which came back positive for papillary thyroid cancer. Then in October 1998, they removed the left lobe which came back negative for cancer. I had no RAI. They put me on Synthroid. I was followed till April 2004 and then released to family

C. DESCRIBE QOL ON THOSE TREATMENTS? **D. APPROXIMATELY HOW LONG DID IT TAKE BEFORE YOU PROGRESSED ON THOSE PREVIOUS THERAPIESS?**		with the brain tumour and had Cyberknife and that was successful. Then I started chemo (Cisplatin and gemcitabine – 1st line) and did 4 months of that. Then I was switched to pemetrexed (April 2014 to May 2016 – 2nd line). Then in June 2016 I started immunotherapy (Pembrolizumab – 3rd line) for approximately 6 months and the cancer really grew. In January 2017 I started Docetaxel (4th line) and was on that till April 2019. In May 2019 I started Vitrakvi."	-In Dec 2014 I received radiation. -In Feb 2015 I had more surgeries and then went to [redacted] in March 2015. - In June 2015 had more surgeries and radiation. -There were lymph nodes in my neck that were identified so I had more surgeries. - And in Jan 2017 did more surgeries to chest and shoulders."	to a Lymph node to the back of my neck. - In Oct 2018: I had 3 weeks radiation to a lung nodule. -In Nov 2018: Gamma knife to 3 brain lesions.		18. I also had adjunctive therapy of hyperthermia through a naturopath which used to last 60 minutes concurrently with the radiation to increase its efficacy by opening up the blood brain barrier to increase the therapy. And finally, I followed a keto diet to help with my cancer and as a side note, my karnofsky scores have always been very high."		doctor who was supposed to test the following: a. TSH, b. T4 levels and c. thyroglobulin. In December 2016, I was really not feeling well and was admitted to hospital who discovered my thyroglobulin had never been tested and was at an alarming 380. In Feb. 2017 I underwent radioactive iodine at 208 millicules. In March 2018 I required another RAI at same dose."
	B. For a bit of time. The thyroidectomy for period of time but mets appeared in 2008. The radioactive iodine clearly did not. The stereotactic radiation did for a bit so overall I guess my therapies really didn't control my cancer because of the mets that appeared in 2008. In May 2016, my neck tumour was removed and it grew back in 6 months!!, which required another surgery which once again wasn't very effective."	"I would have to say that some controlled my cancer more than others. For example, the Pemetrexed controlled my cancer for the longest amount of time – for about 2 years. The others for smaller amounts of time – anywhere between 3 months to 10 months or a year maybe?"	"Absolutely not. My cancer just kept growing and coming back time after time."	"The only treatment that helped to control my cancer, was the gamma knife to my brain. That helped to achieve local control only. Every other treatment really didn't work."	"I think the one that really helped me was the Keytruda. I was able to dance again because I felt so much better. Since my husband had benefits, they were able to pay for it so I was able to get it. Otherwise, I could not afford it."	"I think it is difficult to know because you can't tell with a disease like GBM. I was told that surgery was successful because it was reviewed by two doctors – I had a second opinion. And they said it was an excellent resection. But GBM never really goes away, does it? It was there all along just waiting to kill me."	"No. there was never any tumour shrinkage."	"No, after RAI in 2018, within 2 months my thyroglobulin went up and cancer in my lungs continued to grow."
	C. "Surgical procedures were simple but painful. I healed quickly but the first 72 hours were awful. The beam radiation therapies were the worst. To prepare, they had to put a needle through my face and that was awful! They had to make a mask for the me to undergo an MRI for the therapy. It gave me huge stress and diminished my quality of life. I am now always freaked out when I do an mri. I had a horrible sore throat over the therapy. I couldn't tolerate food after	"Each one of the therapies gave me challenges that I had to deal with. With the chemos, I felt sick and tired most of the time. I couldn't really do much. With the immunotherapy, it was a bit better, but it did nothing for my cancer. The cyberknife really compromised my short-term memory and I can no longer drive."	"I continued to work but took time off during the treatments. When it was limited to my mouth, it was ok, but slowly noticed I felt so tired, I didn't feel right and felt sick, and had loss of appetite. I tried to stay active if I could while on those therapies. I guess my QoL was ok, but I developed issues to my skin, burning, fatigue and I was a real soldier but a lot worse in comparison to Vitrakvi and I had to go to the	"My QoL was not bad. The radioactive iodine was short, but the radiation was **really difficult** because of the pain I had to endure in my throat. The gamma knife was difficult because of vomiting. It was horrible. While I was going through it, it was not great. And the surgeries, well, I bounced back but not fun."	"While on the Keytruda, it was great. But on the others, it was terrible. I was so sickly and shaky all the time. I would feel faint and oh so awful all the time."	"I had a horrible and terrible reaction to the chemo. I was so weak and brutalized by it. I had to come off of it. My energy level has never really been the same because of it. I kept getting more and more fatigued so easily. And I cannot recall words so easily anymore, I guess because of the chemo and the radiation. I tolerated the radiation well though. In addition to the radiation, I took Boswellia, which	"It was poor. I had bad side effects. I had swelling in my legs and feet. I was so fatigued. I had blood clots and was always constipated. I had no zest to live."	"My qualify of life was oh so very unpleasant. It may have been short term, yes, but there were months of leading up to RAI, scans, bloodwork, bone scans, isolated, feeling nauseated, and they kept telling me to not throw up or you will be back in here!. I found it difficult to swallow and eat or drink. My salivary glands blew up. It was horrible."

	that therapy because of the sore throat. I lived on chocolate milk for days because of it. So painful!! I also had to sleep on multiple pillows after that because I couldn't sleep flat. And the same after my surgeries. Horrible quality of life. Therapies also put me into early menopause which was so horrible for me at such an early age. I was having a zillion hot flashes a day. "		hospital a lot. I had surgeries that were dreadful (lost half my beard), my speech became affected wherein I really need to concentrate to enunciate which is very hard and as an attorney, I have to struggle to be understood in court. So, if I had started off on Vitrakvi, I could have avoided a lot of these impairments/ challenges. And I would be in a much better place and not taking opiate meds because of surgeries and radiation due to pain. I work so hard to stay healthy. **I should have had Vitrakvi from the start**. **I was told I was going to die in 3-4 weeks** and then entered the clinical trial. After 4 weeks all my tumours were gone except one which reduced by 65%. It was remarkable."			is essentially frankincense, used as an anti-inflammatory for radiation to the brain. Typically, when patients receive brain radiation, they are prescribed a steroid, (dexamethasone). But I didn't want that. I took Boswellia instead and it was wonderful."		
	D. "I was supposedly disease free between 2006 and 2008 but I was not really disease free because I kept having disease pop up throughout that time that required some type of intervention. Vitrakvi has given me the **longest response**."	"With some I progressed after **3 months**, like the first chemo regimen and others, I progressed after two years, like the pemetrexed – that one gave me the longest amount of time on one therapy. I was on Pembrolizumab for about **6 months** and I was on Docetaxel for about **10 or 11 months.** I have been on Vitrakvi the **longest**."	"I progressed immediately. I **never really** did respond to any of them."	"Between July 2005 and September 2018, we assumed a Watch & Wait approach. The disease was progressing but at a slow pace. There were too many nodules to count in the lungs. It was not good. We did nothing between July 2005 and Sept 2018. Since it was thyroid cancer, there was really nothing to do for it. And I was not really symptomatic. So, I guess to answer your question, I was in a constant state of progression."	"I really can't remember, but I didn't stay on the folfox for very long…I think it was like a **couple of months**. I was just too ill. So horrible…the Keytruda was the best. I was on that the longest. I think I was on that for a **year**. That was the best."	"It was really there the whole time. I was **never really disease free**. That's how GBM works. And you can't really have an MRI after you have radiation. So, I had to wait 3 months at least before having it. The disease acts like a bunch of roots just waiting to infiltrate my brain and head."	"My disease just kept progressing and getting worse. I had no success on those treatments. I **progressed very quickly**."	"After my February 2017 RAI, my lung nodules grew **after 2 months**. And After my March 2018 RAI, my disease progressed after **2 months again**."

9. WAS THERE ANY PARTICULAR ASPECT OF THE DISEASE THAT WAS DIFFICULT TO CONTROL WHILE ON THOSE TREATMENTS?	"My neck and chest disease were really difficult to treat and difficult to respond to with radioactive iodine. "	"At the beginning, the first side effect was hearing loss due to the cisplatin/ gemcitabine which made me have to get a hearing aid. My hips really hurt and my lower back too, but this eventually resolved, except for my hips. My neck area hurt too, and I had to do radiation."	"Yes, my disease just kept growing and never really responding to any treatment. Symptoms were gradually increasing, and I was so shaken by it all, especially after my cruise in December 2016. Tumours kept doubling in size and number after couple of weeks. I was so fatigued and not wanting to be able to do anything because of it."	"My lung nodules were difficult to control because they were never controlled to begin with. "	"Yes, that tumour that developed under my left breast was horrible. It just kept getting worse and I couldn't do anything to help myself. I haven't been able to wear a bra, it had a bad smell cuz it was on the outside of my body. It kept leaking with stuff. It has been just nasty."	"I would say the disease itself. The difficulty with GBM is that it kills virtually everybody that it afflicts. With other type cancers, at least you get a pretty good chance that things can be done to sometimes spare you, but with GBM, I was given 14.6 months of median survival and as a single dad with 3 kids, I am gonna miss my kids and not gonna be able to help them!! There's a clock that ticks above your head: you end up getting chemo, radiation and that's it. And they only buy you a short period of time. You have no hope on that chemo. But I was given hope on Vitrakvi. You have seen what happened to Beau Bidon, Senator John McCain, and Gord Downie: they all died! They lived for a bit, but their time came. My hope was the potential for another treatment, and it was Vitrakvi!"	"I believe the cancer itself was difficult to control rather than any particular aspect of the disease because it could not be brought under control."	"No, I think the disease itself was always a challenge for me to wrap my head around."
PART C: EXPERIENCE WITH LAROTRECTINIB								
10. LOCATION OF YOUR METASTATIC DISEASE?	- Regional lymph nodes in neck - cervical spine - both lungs - mediastinal lymph nodes -hilar & precarinal lymph nodes	"I had metastatic disease in the following area: -My bones (right hip, first 3 vertebrae from the bottom and first vertebrae in neck - brain - liver"	-Lymph nodes in neck, chest, shoulder - Lungs - Liver - Kidneys	-Lungs -Brain - Lymph Nodes on back of neck - Spleen - Liver - Axillary Lymph node - Nodule right muscle behind jawbone	- Brain - Skin (under left breast) - chest wall mass - bones - colon primary intact	"No, doesn't work that way."	"Liver and bones"	"Both my lungs and lymph nodes near my trachea."
11. A. WHERE WERE YOU TESTED FOR LAROTRECTINIB CANDIDACY?	A." [redacted] (Nov.2017) – I was referred by endocrinologist due to advancing lung nodules."	"I was tested at [redacted] and the test went to [redacted]."	[redacted]	[redacted]	"My oncologist had me tested. I think it's called FASTTRK."	"[redacted]."	"[redacted] in Quebec"	"A sample of my lung tissue was sent to [redacted], U.S. in December 2019 by my treating medical oncologist."
B. WAS IT DIFFERENT THAN YOUR TREATMENT CENTRE?	B. "Yes. At the time I was under the care of my endocrinologist who was overseeing my thyroid cancer at [redacted]."	"I guess, since it had to go to the U.S…"	"No. I had already transferred to [redacted] by the time I was being asked to test for Vitrakvi candidacy."	"No, because I was already a patient at [redacted] through self-referral."	No.	Yes.	No	Yes, I am being treated at [redacted], Vancouver, BC

C. THROUGH WHAT TECHNOLOGY WERE YOU TESTED FOR LAROTRECTINIB CANDIDACY? **D. DID YOU HAVE TO TRAVEL TO GET TESTED?** **E. DID YOU HAVE TO PAY OUT OF POCKET TO GET TESTED?** **F. DID YOU HAVE TO WAIT LONG FOR THE TEST RESULTS?** **G. DID YOU EXPERIENCE ANY ANXIETY WAITING FOR THE RESULTS?**	C. "I was tested through Next Generation Sequencing through a trial in November of 2017. It was a 400 gene panel."	"I don't really know since it was done out of country."	"I don't know. They took a biopsy out of my chest (deep in my chest) and it hurt like the dickens to test for it."	"I do not know."	"I have no idea."	"Through genetic testing."	"Genetic Testing through Bayer."	NGS Testing (Foundation One)
	D. "Yes, I had to travel from Allentown to New York City. I took the bus, subway, and taxi. It was a long way, but I did it to try to save my life."	"No, not really. They took a sample and sent it off to get tested. To my knowledge it may have been a sample of my pleural effusion or blood sample. I really don't know."	"No because I was already at the centre as a patient."	"Yes, I had to travel 3.5-hour drive from home which is in Louisiana to Houston. This is a 270-mile drive west of my home."	"No. "	"No."	No	No
	E. "No. the program at [redacted] covered it. The trial at [redacted] covered the cost of testing, I think. I never received a bill, but I do know that my insurance denied the coverage."	"No. I was very lucky. I know Bayer and Life labs are testing for the NTRK gene fusion for patients in Canada, so I assume that's who covered the cost of the test."	"No. I had insurance and had already paid the deductible for that year, so it was paid for by the insurance company."	"No, I did not. I was asked to get tested and my insurance covered the cost."	"No."	"No."	No	No. My medical oncologist started a clinical for the RET mutation so I was covered that way. "
	F. "YES! I waited from Nov. 2017 to March 2018!! It was a long time, but they had to get tumour slides, then there was thanksgiving in the mix, Christmas, so testing was delayed for those reasons. "	"Maybe a month or something like that. I can't really remember exactly. About a month. But once I got approved, it came in very quickly for me."	"No, it didn't take long at all. Maybe 1-2 weeks or so? I received results in January 2017."	"No, I feel like Forest Gump and all good things happened for me. I didn't know how sick I was and lots of good things happened. When the nurse called, she was breathless trying to get the information out because she was so excited for me about the results. I'm so glad I qualified for this extraordinary drug."	"Yes, I feel as though I waited forever."	"Yes, I did. 2.5 months. There were some anomalous results generated and then there was some retesting which delayed the results."	"I waited about 2-3 months."	"I waited 2.5 weeks for the results."
	G. "Oh, for sure! It was very stressful, I worried that I had stuff growing in my body and I wasn't receiving any treatment. I had lots of anxiety. I couldn't wait to receive those results to see if there was something I could access."	"No, I was very excited because it could have been my breakthrough which it turned out to be. I may have had some anxiety, but it all turned out for the best for me. I am so glad."	"Not really. I didn't even know about the clinical trial or drug. Not too much was known about this Vitrakvi. More tissue samples were sent to Arizona for candidacy determination. And that took a week and I felt anxious about that for a bit. I was the sixth person to ever take this drug. Though the history was somewhat successful. I had somewhat anxiety	"Not really. I just didn't know any better."	"Kinda. But I didn't really understand what I was waiting for until it was explained to me again."	"During this time, the pharmacist had approached Health Canada about going on Larotrectinib, but I had to be tested through Foundation One in order to qualify. I had to pay out of pocket to access Foundation One. It cost me $8200 CDN. The results needed to confirm that I qualified for the drug. This was around April 2019. Truthfully, since I qualified, I was happy to pay. I experienced some anxiety when	"Yes, since this treatment was my last hope."	"Yes, absolutely. I have been anxious since 2018."

			over that seeing that not too many people had taken it. But I was certainly willing to try. What did I have to lose?"			waiting for Foundation One results to come back. When they did, I was elated! There was nothing else for me, so the therapy was my last hope. I was NTRK1 positive. It recommended I should have Larotrectinib."		
12. HOW WERE YOU ABLE TO ACCESS LAROTRECTINIB? IE CLINICAL TRIAL? FAST TRK PROGRAM, SPECIAL ACCESS?	"[redacted] from [redacted] called and said I have a rare mutation and I qualified for Vitrakvi through the LOXO trial."	"It was coordinated through Bayer and [redacted]. It was shipped to [redacted] in pill form. It was not a clinical trial to my knowledge but maybe it was, I don't know. "	"I accessed it through the LOXO trial."	"Through the [redacted] Clinical Trial – LOXO 101."	"I don't really know. My doctor saw to it that I received the medicine. It comes to my house."	"I accessed the drug through Health Canada's special access program, and it was in the pill form. Later on, I access it through Bayer's FASTTRK program."	"I accessed it through Bayer."	"I accessed it through Health Canada Compassionate use."
13. A. WHEN DID YOU RECEIVE LAROTRECTINIB (DATE)? **B. AND IN WHAT LINE OF THERAPY?** **C. HOW MANY CYCLES DID YOU RECEIVE?**	A. "I started the therapy in August 2018 at the [redacted] and have been on it since."	"I started the treatment in May 2019."	"I started the drug on January 13, 2017."	"November 8, 2018."	"July 2020"	"Good Friday April 2019"	"December 2019."	"I received the oral solution drug on January 3, 2020 and then started it on January 20, 2020."
	B. "I am not sure, but I guess it would be first line for my metastatic disease???"	"I guess it would have been fifth line therapy and I am still receiving it today!"	"I am assuming it would be considered first line therapy???" I don't really know."	"No really sure."	"I don't know. My husband was keeping track while he was alive but according to his records maybe it would be fourth line?"	"I guess since it is after chemo, it would be 2nd line. I don't really know."	"Third line."	"First line therapy. "
	C. "I am still on Vitrakvi today with no interruptions. I don't know how many cycles that is but still going strong! It has been well **over two years**."	"I have been taking it every day for **18 months** since I started the treatment. I started on pills but then switched to oral liquid form. I have never missed a day except for 2 days when I had a blood clot in my left lung which was not due to Vitrakvi but I did have to stop taking the drug for 2 days because of it. It's protocol."	"I am still on Vitrakvi today. **40 some odd cycles.** This is the **longest therapy I have ever been on**. And I hear I have been on the drug **the longest than anyone else!!** I have been on it **3 years and still going.**	"I have received **25 cycles** and I have never missed a cycle or pill. I continue to receive the therapy today. I have been on it for **two years now** ."	"I don't know how many cycles, but I have been on it since then and I haven't missed any medicine except for when I was in the hospital."	"I have lost count. I have been on it for **19 months**. All I know is I have not stopped. I take it twice a day with breakfast and dinner. At first, I used to take a capsule but now I am taking the liquid form of the drug. But the liquid form of the drug had its limitations because it has to be refrigerated at all times. So, I am restricted cuz I have to get back to refrigerator when taking it. In case there is a power outage, I keep one dose at my place and another at my dad's. Travel is out of the question for me and my children, so I hope to gain access to the capsule form soon."	"I think it is about **nine cycles**. There were 2 times that treatment was stopped so they could determine whether treatment caused my red cell anemia. They determined the treatment was not the cause. And I was not treated for anemia."	"It gets a little complicated here. I was taking 10 ml per day in January, February and March. Then noticed that my ALT liver enzyme was significantly elevated, so they took me off the drug for 10 days and the withdrawal pain was awful. Then restarted on 8 ml/day. That lasted to April 29/20 and then ALT went back up. So I was taken off medication again. Went back on May 10/20 and off till May 20/20. I went back on it June 6/20 at 5ml/day. I have been on that dose ever since. By the end of this month, I will be completing **bottle #21.**

14. BASED ON THE THERAPIES YOU RECEIVED PRIOR TO LAROTRECTINIB, HOW LONG (IN WEEKS OR MONTHS OR YEARS) DID YOU RESPOND TO EACH OF THE THERAPIES YOU RECEIVED FOR THE TREATMENT OF YOUR CANCER?	"I received small increments of response to the surgeries and radiation, but I never really had a great response where I was disease free for a long time or responding for a long time to the therapies. I guess I would have to say that between 2004 and 2008, I may have had 6-9 months where I may have had periods where my disease was somewhat under control but I have to say, looking back that really wasn't the case. Vitrakvi has provided me with the **best response and longest response**."	"So far, this therapy has given me the second longest response next to pemetrexed. But I have to say**, I sort of think it's going to surpass the response I receive from pemetrexed** based on how I am feeling and how I am responding. Or at least, I hope so. Scans have shown great results. My cancer has stopped growing or at least is stable. Some tumours are not there anymore. And there is no new cancer at all!"	"I never really had a good response to any of the previous therapies. My tumours just kept growing and spreading which is why I am so happy to be on Vitrakvi. I became so ill where I was given a timeline for death. This **therapy (Vitrakvi) has given me what I really needed** to bring my disease under control."	"Except for the brain lesions, my disease has **never responded** to the treatments I had. And I had a lot of disease that was difficult to control, especially the lung nodules."	"I didn't really have a good reaction to anything except Keytruda. That's the only medicine that I had a good reaction to and this one too. I think I was on it about **a year**. Everything else was not effective for me. My doctor said I have a specific type of cancer that contains a certain mutation and has to receive certain types of medicines. I have something called MMR-D cancer. And I also have another mutation which is why I am on this medicine."	"I was on the chemo and radiation for approximately **one month** but had to come off of the chemo because of low platelets. So, I really had no response to those therapies."	"My prior therapies showed **no response** whatsoever."	"**Nothing worked** for me. My disease progressed on every therapy I have been on before larotrectinib."
15.A. HAVE YOU EXPERIENCED ANY SIDE EFFECTS WHILE ON LAROTRECTINIB? Y/N **B. IF SO, WHAT ARE THOSE SIDE EFFECTS?**	A. Sort of.	"No, not at all."	"None, but…."	"Yes."	"Yes"	"None! Except for elevated liver enzymes according to my doctor (AST and ALT) but after adjusting water intake, it has improved. I went from 2L to 4L intake and they have improved. ***Oh, and by the way, the muscles on the side of my face are sore from smiling so much cuz I'm on Larotrectinib!"***	Yes.	Yes.
	B. "Some mild ones. At the 3-month mark, I had some facial sensation, nerve sensation that felt prickly, but it wasn't constant. I also experienced muscle aches and stiffness, again not all the time and I think this was a withdrawal symptom, as I was nearing having to take my next dose. I had burning sensation in my chest. Ear pain that eventually went away. But all of these were quite mild and typically occurred 4 hours before my next dose, as the drug is wearing off. But I	N/A	"But there are withdrawal symptoms such as aches in my body or cramping just shortly before I am scheduled to take the next dose. But as soon as I take the drug, I am restored. It is so much better than dealing with surgery for example. I had some cosmetic surgery and had to stay off he drug for 10 days, so withdrawal was bad for 3 out of the 10 days. "	"I have been luckier than most people. The only side effects that I have had are skin tenderness at the beginning when fabric touches my skin, but it went away. And there was a surge after 45 minutes or overstimulation , but its better now too. If I am late taking my dose, my muscles ache. Otherwise, I haven't experienced anything."	"When I first started taking the medicine, I was on 5ml of the liquid medicine. I could not feel myself. I know that sounds weird, but I felt so unsteady and I needed a cane to hold myself up. I even passed out. And I went to the hospital cuz I was unconscious. So, my doctor put me on a lower dose (1 ml) and then the side effects went away. He then increased my dose to 5 ml. I'm good now."		"Just some moderate tiredness."	"I developed a minor cough as soon as I started the drug. I don't really know if it was due to the drug or the lung mets. And I also developed fatigue about 6 months into the therapy. But I feel the fatigue here and there when I am doing gardening for example at certain points during the day."

	am quite happy because in comparison to other therapies, such as chemo, which I have not been on, but based on what I have heard can be so brutal, my side effects are a walk in the park."							
16. ON A SCALE OF 1-10, HOW WOULD YOU RATE YOUR QOL WHILE ON LAROTRECTINIB? 1 REPRESENTING VERY POOR AND 10 REPRESENTING VERY GOOD QUALITY OF LIFE.	**8**	**8** "I have a hard time walking and dizziness but it's **not due to Vitrakvi**. I am also tired. This is all due to the chemo I have had in the past. If it weren't for all the chemo stuff, **I would have rated my QoL a 10**"	**10** "Absolutely wonderful. My energy is fantastic, and I have more now because it puts me in my original shoes **as if I don't have cancer at all.** I have a great lifestyle. I don't feel sick while on it. I am a productive member of society. I wish I had been put on this drug from the beginning and avoided the other therapies."	**10** "**It has been great being on this drug."**	**9** "My life is good while on this medicine. I have no complaints except for the way the medicine is delivered. The box is so hard to open. It is annoying and heavy and challenging for me to open. I would really prefer to have the pills instead of the liquid form."	**10** "My experience with chemo was so bad. I was so nauseous all the time. I had to take other medications just to take the chemo. Ie Metonia. Which is an anti-nausea drug and even with that I felt terrible. When compared to Larotrectinib, it's like 2 completely different universes. One makes you feel like you have the worst flue possible and the **other like you're drinking a cup of water**. "	**6** "There is certainly an improvement over my previous therapies."	**8** "I have a very decent life with Larotrectinib, each day with family and friends. I get to walk the dog every day, go grocery shopping, have massages twice a week for my nerve pain. More than anything, COVID is really the problem not Larotrectinib. My quality of life is really good. I can do things now that I could not before. Larotrectinib has given me time and hope that I did not have before. I believe I have many years with this treatment."
17. DID YOU HAVE ANY CANCER SYMPTOMS BEFORE STARTING LAROTRECTINIB? IF SO, WHAT WERE THEY?	"Yes. The lump on my neck really hurt. And walking was so hard for me. I couldn't exert myself. And I wheezed all the time."	"Painful hips and poor appetite."	"Yes. I had fatigue, general malaise, muscle aches and cramps, lack of control of body functions, pain from cancer treatments."	"Ya, one really bad nodule in my lung started to grow and caused wheeziness at night, coughing up blood. I had shortness of breath too."	"Yes, that terrible thing under my left breast – it was gross and growing, and oozing, and it was so stinky. It was so hard to control. I had to change the bandages all the time throughout the day."	"No, not really."	"Yes, I had some pain."	"Yes. Shortness of breath in November 2019 which was severe. Going up the stairs and walking the dog up the hill was impossible for me. I couldn't do it."
18. IF YOU DID HAVE CANCER SYMPTOMS BEFORE STARTING LAROTRECTINIB, DID LAROTRCTINIB HELP RESOLVE THOSE CANCER SYMPTOMS? IF SO, WHICH ONES? PLEASE EXPLAIN.	"Yes. My huffing and puffing went away. The lump in my neck resolved, I couldn't feel it anymore. My walking improved and the wheezing resolved as well. I have to tell you that these resolved almost immediately after starting Vitrakvi."	"Overall, things have improved since I started Vitrakvi. Even my appetite has improved, and I have returned to normal after years of fighting chemo-induced metallic tasting food and just loss of appetite and now I have also gained my weight back because of Vitrakvi. My hips don't hurt the way they used to either."	"All of them have resolved except the pain induced from cancer treatments."	"I believe the drug has kept the lung nodule from coming back. I developed a small bump in my leg and another in my calf muscle and both disappeared in days from starting the drug therapy. "	"It sure did. It got smaller! Now it's no where near as bad. And it doesn't smell as bad and it doesn't ooze nowhere near as bad. This is all due to the new medicine I am on."	"N/A"	"Yes, I was put on pain meds and now because of the treatment, my doctors are looking to reduce my pain medication at my next clinic visit."	"Definitely. My shortness of breath has resolved. Now I can walk the dog up that hill and do the stairs in my home."
19. A. HOW WAS RESPONSE CONFIRMED TO LAROTRECTINIB: CLINICALLY (SYMPTOMS	A. "Through CT scan. And through thyroglobulin testing too I guess. Clinically too according to me	"MRI for my brain. CT for chest, abdomen and pelvis. Bone Scan for my bones."	"CT scans every 3rd cycle. Bloodwork full range, urinalysis."	"MRI to brain and CT scans."	"I think it was because of the CT scans I have been having."	"Through an MRI with contrast. Before it used to happen every 2 months now every 3 months. "	"CT Scan and Bone Scan."	"CT Scan. "

RESOLVED), BIOCHEMICALLY, OR RADIOGRAPHICALLY (SUCH AS CT, MRI)? **B. WHAT WAS YOUR RESPONSE TO LAROTRECTINIB?**	though they didn't pay attention to that. But I did because I could see that I was feeling better and that mattered to me so much. My life was improving. I could get around and do things that I couldn't do before."							
	B. "All my tumours responded. They all shrank in the first 1-6 months. It was a **miracle** almost. I have been stable or the tumours have been shrinking since then. I think my overall RECIST reduction has been approximately 50%."	"Like I said before, my scans have shown great results. My cancer has stopped growing everywhere in my body or at least is stable in some parts. Some tumours are not there anymore. And there is no new cancer at all. I have had a great response to this treatment."	"I had the most **extraordinary response**. I had so many tumours – they couldn't count how many tumours I had in my lymph nodes, liver, kidneys, etc. and they certainly couldn't remove them surgically. I remember, at one point, they had doubled in size and number in just 5 days. They were growing and spreading so fast. I recall being so ill in hospital bed just before starting this Vitrakvi. I was told **I had 3-4 weeks to live**. I couldn't even sit in a chair. - that is how ill I was. They started me on the drug and in just one week, I felt remarkably better and I kept feeling better and better after that. I could feel the lumps on my skin reduce to nothing. After the 4th week, I couldn't feel the lumps anymore. After the first CT scan, **all my tumours were gone except for one which had shrunk by 65%.** And that lung tumour continued to shrink that year. Now that tumour has disappeared and is merely scar tissue. **I no longer have any sign of cancer detectable through CT**. and there have been no new tumours. I am a **NED patient** because of Vitrakvi. I am	"I have had **49% tumour shrinkage** according to the CT scans. As for the thyroglobulin: mine climbed to 50 and then to 257 in 2015 and now it's at 42 because of Vitrakvi. If the tumour shrinkage rate wants to stay at 49%, I would be very happy with that. Nothing has popped up at all. It's wonderful. So, it could continue to shrink but I am happy if it just stays stable."	"Well, I can tell you that the medicine has been working because of the lesion under my breast. It has gotten so much better. Plus, my doctor tells me that the medicine is working."	"I started the drug therapy in April 2019. In June 2019, the first report said there were only 2 nodules there which was pretty remarkable. **BUT SINCE THEN FILOMENA, EVERY SCAN HAS SHOWN UP CLEAR. THERE HAS BEEN NO EVIDENCE OF DISEASE DETECTED. All my doctors are cautiously optimistic. Since GBM is so veracious, I must stay on Larotrectinib. It is my lifeline**!!"	"My CT Scan from 6 months ago revealed no liver metastases. The scan from 3 months ago showed one small spot on the liver. Otherwise, I **have no more disease. I have experienced a complete response"**	"There were 2 lung nodules that were used as markers. After just 2 months of being on the therapy, this is what they observed: One nodule went from being 2.3x2.0 to 1.8x1.6cm with a volume reduction of 37.4%. And another one went from being 2.6x1.6 cm to being 2.3x1.5 cm with a volume reduction of 17%. I was so happy. All other nodules were either stable or reduced! "

			fully restored. I **work full time, manage 50 people, have an active litigation practice and live life to the fullest**.					
20. DID YOU HAVE TO STOP LAROTRECTINIB? IF SO, WHY?	"No, not at all."	"No, other than those 2 days in the hospital for the blood clot which was not due to Larotrectinib."	"Only for cosmetic surgery (10 days) – that's it."	"No."	"Just when I was in the hospital for 4 days. That's it."	"No, not once. "	"Yes, I had to stop twice. 4 weeks from April 14 to May 12 and In August for 3 weeks due to anemia but the anemia was not due to the treatment and they never did find out what the anemia was due to. They never treated the anemia. It went away by itself."	"Yes. Due to elevated liver enzymes. But after reducing my dose, I am now back on the drug."
21. HAS LAROTRECTINIB BEEN EASIER TO USE THAN PREVIOUS THERAPIES? WHY OR WHY NOT?	"Yes, because you're swallowing a pill twice a day in the comfort of your home whereas in comparison to radioactive iodine where you're isolated and following a strict diet, it's very different and oh so limiting and awful! It's so convenient and easy to use."	"Oh ya, the syringe in my mouth is an easy squirt – it's so easy and great. So convenient, much better than the chemos I had to endure. It even tastes good, surely good for adolescents and children. Saves me lots of trips to the cancer center, saving money and time and effort and a lot of stress. What could be easier than this treatment?"	"It most certainly has. Mostly because it is an oral therapy. You can take it with you anywhere and there are no trips to the hospital in order to access it. Expenses are significantly reduced. I am so much better off because of this lifesaving therapy."	"Oh, yes, for sure. It is definitely easier than surgeries and radiation. I can sit at home, take a pill at 9:45 a.m. with water and go on my way. Next dose I take is at 9:45 p.m. It is so easy. "	"No, not really. It has been a pain in my behind…. filling the syringe. It's a small syringe with small numbers and having to program my phone to take it. It's awful. Sometimes I need my PSW to help me. I really need the pills please. That would be so much better. Can you help me? This way I can add them to the blister pack. Then everything would be perfect."	"Yes, I don't throw up at all. Or feel like I am completely sick. I love it."	"Definitely. This oral therapy is easy to take, especially since it is a liquid."	"Absolutely. The side effects are very tolerable. I can do so much in my days like cleaning the house, or shopping, or walking the dog. I couldn't do these things before. I have my life back. The drug itself is in liquid form. I just pop it in my mouth and off I go. It's a bit difficult to open, but once it's opened, it's ok."
22. WAS IT WORTH ACCESSING LAROTRECTINIB? WHY OR WHY NOT?	"Of course, it was! First of all because it shrank my disease. Did I have any other options at the time? But now knowing that I do, it has been the best option for me. It has been such a wonderful therapy for my disease because it targets my disease based on the unique genetic characteristics of my disease."	"Oh, ya for sure, it saved my life, where would I be today? I needed something and my doctor got me on it asap and I have been on it since. It has been amazing. I started to feel better so quickly. The side effects from chemo and radiation left almost immediately even though I have some lingering effects. I wish I could have been spared dizziness, short term memory loss and so much more from the other therapies I had to endure. This is a therapy that spares patients from toxic effects. I have had to give up driving because of brain radiation affected	"Without a doubt. I would be dead today were it not for this drug. It has literally saved my life. How do you assign a price tag on something like that?"	"Yes, even at the time since I didn't know any better, I had life threatening disease, it has given me a new lease on life. Who knows what my longevity would have been? I now have my life and good life back. "	"Yes. The lesions are not stinky anymore or as my doctor put it, aggressive like before and I don't have pain anymore and the best part is I haven't died! On February 11, 2020, I was told I had 6 months to live, but here I am still alive because of the medicine. Just goes to show you what a good outlook and a good medicine can do."	"Absolutely. Without a doubt. Because without it, I would likely not be here today. Without it, there is no hope for me or my 3 children. They would not have a parent.!"	"Yes. It has provided me with renewed hope."	"Yes, of course! Very easy to administer and tolerate. Others go through terrible things and side effects, but I am so lucky. My side effects are nothing in comparison to others'. It truly is a miracle drug. I am here today because of this drug."

		cognitive skills and memory loss. I just didn't want to kill someone or myself. This could have been avoided had I been able to access Vitrakvi. Others can be spared this."						
23. DID ACCESSING LAROTRECTINIB ALLOW YOU TO FULFILL OR ACCOMPLISH ANYTHING IN LIFE THAT YOU WOULD NOT HAVE OTHERWISE BEEN ABLE TO DO HAD YOU NOT ACCESSED THE THERAPY? IS YES, PLEASE EXPLAIN.	"I am able to live today because of this therapy for the most part. And it's a normal life that I live. I can manage through it for the whole day. I probably would have died were it not for this therapy. It has given me more time to live and enjoy the things I love to do and spend time with the people I love. There is no greater gift than that."	"I sure did. Because of Vitrakvi, I got to celebrate my 60th birthday and lots of people were in attendance and I saw the birth of my grandson who I adore. Because I am responding so well to the treatment, I get to spend time with that little guy. I set goals for myself now that I am on Vitrakvi. I got to attend my daughter's convocation from teacher's college. I have been able to get back in shape. My son is getting his first house. These are joyous moments I get to share in because I am well enough to do so."	"For sure. Look at what I am able to accomplish, produce in life because of Vitrakvi! Instead of being in a hospital bed, I am cycling, running and arguing cases in front of juries and feeling so very healthy and doing it with so much zest. Even if I had survived on other chemos, I would be doing it with so much fatigue and toxicity, it would not be the same. I get to go out and enjoy life at restaurants, theatres, I travel, (COVID notwithstanding) and I enjoy the company of my family and friends. I genuinely contribute to life."	"If it weren't for this drug, I would have more worry and concern, so I appreciate being part of something big and great. I give my blood for the sake of science. I get to celebrate every day and do normal things which is so extraordinary. There is extraordinary in the ordinary. "	"This medicine has helped me enjoy my life and spend time with my family like my grandchildren. It has improved my quality of life. It has made my life so much easier. Because of this medicine, I am able to spend time with my children (my boys) and my sweet grandchildren who bring joy to my life. They are so active and some days I can keep up with them. I could never do that if I was on a medicine like folfox."	"Yes, how about being alive??? And I have been able to work on a YouTube channel for GBM patients for Larotrectinib testing and things they can do to access help. I am strong today because of this drug therapy. I have gotten to parent my 3 kids. That is the greatest privilege of all. The drug gives you life and the ability to live. Without this, you would have horrible progression of GBM. Instead, the drug allows you the ability to get back to your life. What a gift that is!"	"Although the pandemic has not permitted me to do all I want, this treatment has allowed me to spend precious time with my wife and family – time I would not have had otherwise. This has been a gift."	"This drug has given me time with my family and friends. Time that I don't think I would have had otherwise. It has allowed me to live longer and it has brought me hope every day that I have been alive. "(***Became emotional…..)***
24. WHAT IMPROVEMENTS WOULD YOU LIKE TO SEE OVERALL IN A DRUG THERAPY THAT ARE NOT AVAILABLE CURRENTLY IN OTHER THERAPIES?	"A therapy needs to keep you at least stable and give you good quality of life and that therapy would be a win-win therapy if it could also shrink your disease."	"Besides extending life, it has to improve or maintain quality of life. I can't go back to work because I have lost some skills as a result of the therapies I have been on. That is horrible. Those are terrible therapies that diminish quality of life."	"It needs to be an oral therapy that promotes QoL and restores energy allows you to live a full life. Prolonging life alone is not enough. It has to promote your quality of life and I must say that **Vitrakvi hits the ball out of the park for this**."	"Allows you to be the person you want to be and not a cancer patient. It should make you forget about having cancer. Yes, it should shrink cancer and be symptom free and maintain it. And it should for a very long time not just 2 years."	"I would like to see a cure. My doctor is so great, and he promised my husband that he would do everything he could for me. And to date, he has which is why I am here today. He saw to it that he got me this medicine which I am on today. I would like to see a cure even if not for me, for others who come after me. Everyone deserves to live life and get over this terrible disease."	"For other drugs? It should provide you with quality of life, which my chemo did not give me. So, while you are alive, you really should be able to live while undergoing treatment. The treatment should also target your specific disease, for example if you have a specific mutation, you should be receiving a treatment that targets that mutation and it should not be toxic. The side effects should not put you into bed. And the treatment should buy you lots more time, not just weeks. The treatment should treat the patient, not the	"A therapy that does not have bad side effects and improves your everyday living."	"I would like to see a drug that can be taken in a pill or capsule form. One that is easily opened and has little to no side effects and of course can prolong patients' lives if not cure them altogether. Their quality of life has to be improved so that they can live life to the fullest."

						disease. The treatment cannot be worse than the disease. Otherwise, what's the point? And finally, make the treatment in a form that allows me mobility ie pill form (capsule) allowing for travel and mobility."		
25. WOULD YOUR LIFE BE ANY DIFFERENT IF THE DRUG THERAPIES HAD THOSE DESIRED IMPROVEMENTS?	"Yes, because I could have avoided harmful radiation and unnecessary surgeries and anesthesia."	"Yes, for sure. Because I have a grandson I would like to hang out with, and I can't because of dizziness due to whole brain radiation and I can't keep up with him. "	"Well, my life wouldn't be any different because **my drug already does this for me**!! For other people and other drugs, I wish they could do this. Yes, so many are sick. Other cancer therapies should be as successful as this one."	"I am hoping that the therapy I am on actually has these improvements."	"Of course, it would be different! I would be working and would not be stuck at home crocheting or doodling! I was always the life of the party and actively doing something for others. Now, I am so dependent. A cure would allow me to go back to my old life but with a greater appreciation for what I have been through."	"Of course, it would."	"Yes, certainly. Not having to deal with multiple side effects would certainly have a positive effect on day to day life."	"Oh my, of course it would. My life would be wonderful if they had all these qualities. It would be perfect actually. I would probably have gone back to work. I am in my prime. It would change my life." (***became emotional….)***
27. DO YOU BELIEVE LAROTRECTINIB HAS THOSE DESIRED IMPROVEMENTS? WHY OR WHY NOT?	"**Yes!** And I am living proof of it. I know others on it as well. We share stories/journeys (good and bad) consistent with the profile of the drug. We compare and see that this therapy shrinks and provides good QoL for patients."	"**I do.** I believe it has helped me with quality of life and stopping my cancer from growing. I do not go to the doctor every week. I take an oral therapy which is great. I get to do more things with family and friends. If I had started it earlier and avoided the other toxic therapies, this would have been ideal for me!!"	"**Oh yes**, it sure does. Vitrakvi is what gave me this idea to answer your question. It **has done more than save my life. It made me feel good again**. It has gone beyond what most people experience and would expect from a cancer therapy. **All cancer therapies should aspire to this. "**	"**Yes,** Absolutely. The longevity, well, I am not sure yet because it hasn't been the case for everyone, but I am hopeful it will be for me. Because I am coming up to two years now and I am still responding. "	"I sure hope so. Don't you? Right now, I can't say, but I really pray all the time."	"**Absolutely**. Except for the fact that the drug is in the liquid form."	"**Yes, it does**. This treatment has minimal side effects."	"**Yes, absolutely**, most of them. It has given me great quality of life. Few side effects. It's an oral therapy. Easy to administer. I believe it will extend survival for me."

28. DO YOU WISH TO ADD ANYTHING ABOUT WHY ACCESSING LAROTRECTINIB IS SO IMPORTANT TO PATIENTS AND CAREGIVERS?	"Yes. It is extremely important this therapy be made available to patients who qualify. It will save lives and avoid unnecessary toxic treatments that could have harmful repercussions. This therapy could give patients good QoL and is easily administered. It shrinks disease, it's easy to use at home. The drug allows patients to live with acceptable QoL amidst their families and friends and it extends past the patient and into the community as well, for the patient's wellbeing impacts so many other's lives when the patient is feeling well and able to be a contributing member of society. This therapy should be approved and made available to those patients who qualify."	"This treatment gives a patient a second chance at life. By the time you get to Vitrakvi, you're at the end of life. It shouldn't be that way. It stops your cancer and gives you a new lease on life and this is precious. I am so, so grateful to Bayer to be on it and all the people involved who helped me get on it. There are lots of people asking me about it and what this therapy does. I tell anyone who is willing to listen. Let's get this treatment approved for those who need it. People just like me who wouldn't be here today were it not for this extraordinary treatment."	"Vitrakvi is not like your normal cancer treatment. I know it's an expensive treatment but it's cheaper when compared to what was spent on me before I had Vitrakvi – over half a million dollars! This drug stops the cancer before it starts. It's an amazing discovery. Why wouldn't you want to do this? This drug has given me a second chance to be myself at 100% and my natural energy as well as enjoy life to the fullest. I can't tell you how grateful I am. It is so humbling to be told you have 3-4 weeks to live and then given some hope to live longer and then given more time and longevity. It is a wonderful experience, one that others should be given as well. I truly wish that for others too!"	"For patients, another therapy that is the best to shrink their disease and help them live is critical. Vitrakvi is helping to revolutionize the way cancer is treated and first to treat a mutation across various cancer types. For caregivers, it helps to normalize the family's life so that patients and family don't have to go back and forth to the hospital because it is so conveniently administered. Patients will be part of something bigger that will help generations to come! We will all think back and say, "***REMEMBER WHEN VITRAKVI CHANGED THE WAY CANCER WAS TREATED***?"	"This medicine can give you a second lease or chance on life and can shrink your cancer. When it does that, it can improve your mindset and gets you out of a bad depression. Overall, it can improve your quality of life. It can help you with so many aspects of life. Because of this medicine, I finally got to sleep on my side the other night it was actually ok! I maintain a good outlook because I am doing good on this medicine. I put makeup on every day, and I want others to have this medicine too so that they can be helped like me and it should be free for everyone."	**"**I sure do. With respect to cancer care, drugs attack the entire body, produce different side effects and the drug itself does lots of harm to the body. This particular drug however, works extremely efficiently in anyone who has NTRK1, 2, 3. I feel it would be criminal to not provide the drug to the 1% of patients who have the NTRK1, 2, 3 marker. The drug has an overall response of 75% efficacy and 25% of complete eradication. It works on all solid forms of cancer that have these markers. In the case of GBM, there is nothing that is called a cure, nothing that can be done, and anyone diagnosed quickly learns that this is a death sentence. Occasionally a famous person will be diagnosed with GBM (ie Gord Downie, Senator John McCain, Beau Biden) who draws our attention to the disease. The rest of the time, our attention goes away from GBM and these patients die in silence. This is the first drug ever that has the potential to slow down, stop or even completely cure these patients. And as an individual who is walking this path, I can tell you that there is no hope unless you have this marker and if we were not to approve this drug, it would be the same as if providing a death sentence to these people when we	"This treatment has given me renewed hope with minimum side effects. Others should have that chance too."	"Having an NTRK mutation is rare and I am so blessed that I have been able to access this **miracle treatment**, giving me more time. It is a drug that has few side effects and able to allow me to do so much with my life. It truly is a life saver. Please give others the same hope for life. We owe them that, it's the humane thing to do."

						hold a potential cure in our hands. This is not a hyperbole. This drug is a necessity for all those who can take it regardless of cancer type. It took more than 20 years to make this drug a reality. Years of testing and now it is here in our hands. I cannot imagine any reason why we would deny anyone a drug with such a high overall response and zero side effects. Please reimburse this therapy."		

TABLE 2: LAROTRECTINIB RESUBMISSION: PEDIATRIC PATIENT & CAREGIVER INTERVIEW HIGHLIGHTS

INTERVIEW QUESTION	PATIENT I	PATIENT J	PATIENT K	PATIENT L
PART A: DEMOGRAPHICS/INFORMATION GATHERNG				
1. INTERVIEW DATE, TIME & METHOD	30 Oct 2020, 8:30am BST, E-mail	October 30, 2020 3:00 p.m. EST Email	October 15, 2020 Zoom	February 2019 Telephone
2. PATIENT'S AGE & GENDER (M, F)	Age 3, Female	15 years Male	Interview Parents Currently 11 years, Sixth grade	Parents Interviewed Son, Male
3. CAREGIVER UNDERGOING INTERVIEW	Mother	Mother	Parents	Both Parents
4. CITY & COUNTRY	Newtownabbey, Northern Ireland, United Kingdom	Ludington, Michigan, USA	Calgary, Alberta	British Columbia
5. TREATMENT CENTRE	[redacted]	[redacted]	[redacted] (Primary) [redacted] (Secondary)	[redacted]
PART B: DISEASE EXPERIENCE & EXPERIENCES WITH CURRENTLY AVAILABLE TREATMENTS				
6. A. TUMOUR TYPE	A. Infantile Fibrosarcoma	Thyroid Cancer	Thyroid Cancer	Thyroid Cancer
B. DATE OF FIRST DIAGNOSIS?	B. September 2017	January 21, 2014	"In 2014, at 4 years old, we noticed a lump on his neck; however, it did not go down after a couple of weeks. he went in for	"At the age of 12, he came to his parents noticing that he had a lump on the right side. Sometimes would have strep
C. IF APPLICABLE, DATE OF METASTATIC DIAGNOSIS?				

			an ultrasound and about 30 or so lumps were found on both sides of his neck. A biopsy was done, and it came back positive as cancer. A chest x-ray was done and more imaging of his neck and lymph nodes. Tumours were throughout the body and wrapped around the heart. He was diagnosed with stage IV thyroid cancer. He had just started kindergarten and had also just started hockey. He is an active boy with lots of energy. Hospital had never seen kids with thyroid cancer before. Their doctors consulted with doctors all around the world and even consulted with doctors who had treated children from Chernobyl."	throat. Parent took him to the walk-in clinic and thought it was unusual. Did some follow-up tests and waited to hear back. Went to get the blood work done and that evening received a telephone call. About a week from beginning to the call. Went to [redacted], and were told to go to emergency. Went to see oncology and endocrine. It was diagnosed as Thyroid Cancer."
	C. N/A	January 21, 2014	Metastatic at diagnosis.	
7A. THERAPIES RECEIVED BEFORE LAROTRECTINIB? **B. DID THOSE TREATMENTS CONTROL PATIENT'S CANCER? Y or N (Explain)** **C. DESCRIBE QOL ON THOSE TREATMENTS?** **D. HOW LONG DID IT TAKE BEFORE PATIENT PROGRESSED ONTHOSE PREVIOUS THERAPIES?**	A. "Vincristine & Actinomycin September 2017 – December 2017; Ifosfamide January 2018-March 2018; Doxorubicin & Ifosfamide March & April 2018"	"Thyroidectomy and 2 bilateral neck dissections. Two radioactive iodine ablations, one of 91 mCli and another of 300 mCi.."	"In December 2014, he had surgery to remove the tumours at the [redacted] He had cardiac, thoracic and ENT surgeons conduct the surgery. At six months old, he had open heart surgery and there were concerns about the healing from this surgery and how it could complicate the surgery to remove the cancerous thyroid tumours. That is why there were so many specialist surgeons in the room with him at the time of this surgery. Recovery from the surgery was long and the family stayed about a month in hospital. The next phase of treatment was Radioactive Iodine (RI). At this point, he was 5 years old and it was approximately February 2015. This had not been administered in a children's hospital before, so they brought over lead shields to create a make-shift room. The ICU nurses were provided training for the RI treatment. At this point, his mom had just had a baby and she was unable to be with him due to the radioactivity. I, his father, stayed with him in hospital for the 5 days until it was safe for him to return home. When he returned home, there were a lot of precautions to follow in terms of taking care of him due to the small amounts of remaining radioactivity from the RI therapy.	"Surgery and radiation. Second surgery and more radiation."

			Thyroid cancer releases a protein. At diagnosis it was 16,000 but after RI it came down to 5,000. November 2015, RI therapy was done again; however, this time he was taken home to his Grandparents home so that he was separated from his family. The family created a great space for him in the basement where he would be happy. "	
	B. "There was initial reduction in tumour size on all three regimens but the tumour never disappeared and indeed started to grow back during the first two regimens."	"No. His cancer continued to grow after all treatments. The surgeries reduced the bulk of the disease in the neck, but nothing helped the lung metastases."	"Not a lasting response."	No
	C. "My daughter suffered awful eczema during the months of all three chemotherapy routines. Her skin was inflamed, sore and itchy and flaking off. This was a real infection worry and she did have an infection in her Broviac line probably due to skin issues. She had trouble sleeping because of the discomfort which affected the whole family. She did not gain any weight for the first 5 months of treatment and had a range of allergic reactions to food. Her albumin levels were alarming, and she had oedema. There was real failure to thrive. She was physically weak and could not crawl or walk or meet other physical milestones until chemotherapy ceased. She was regularly an in-patient in hospital due to infections and nutritional issues. We spent weeks on end in hospital which seriously affected her quality of life and her ability to develop."	"Surgery caused the loss of my son's thyroid and parathyroids. He now has chronic hypothyroidism and hypoparathyroidism along with hypocalcemia."	"He didn't experience many side effects from the RI – only a change in taste buds and he was a little more tired than normal."	"Was operated on within a week and had the lump removed. Had all of the risks explained to them about the challenges of the surgery. Everyone was really good about giving them information and keeping them in the loop. Their son was involved in all of the conversations. He became an active participant in his care team. After the first surgery, did have a small amount of radiation, thought that they were good and would just have endocrine appointments as he didn't have a thyroid. He would have blood work on a regular basis."
	D. "Only a matter of months. An X-ray on 2nd Jan 2018, showed progression during VA regimen and an MRI scan in March 2018 which showed tumour progression during Ifosfamide regimen after only two months."	"There was immediate progression after each therapy found at follow up appointments."	"In the summer of 2016, his breathing changed in the same way that it had changed after surgery. We knew that something wasn't right. He was struggling to play hockey and didn't have his normal volume/capacity due to lack of oxygen. It was found that the cancer had grown into his lungs. He began to rely on supplemental oxygen when he felt that he was struggling to get enough oxygen. HIs care team looked into the possibility of another RI	"Almost one year."

			treatment; however, he had already had two large doses, getting close to reaching his lifetime maximum. They thought about doing small dosing. However, it was found that his cancer was no longer absorbing the radioactive iodine which no longer made it an effective treatment. In May 2017, the family was exploring all options. Was approved for levatinib, tried the therapy and saw some improvement but then progression."	
8. WAS THERE ANY PARTICULAR ASPECT OF THE DISEASE THAT WAS DIFFICULT TO CONTROL WHILE ON THOSE TREATMENTS?	N/A	"The disease was never stable on previous treatments."		"Almost a year later, his testing came back saying that he still had cancer. Had to go back and do a second surgery to remove the cancer. The second surgery was much harder on him. Going into grade 8, 13 years old, and self-conscious about the scar. He was no longer playing soccer since he didn't have the endurance. He was taking medication for his thyroid. Harder for him to get back into routine, stopped playing sports and he stopped associating with many of his friends as he didn't want to answer questions about his treatment. He kept everything inside and didn't want to explain to people what was happening to him. More challenging the second time around. Gained weight, 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. Became a pescatarian – fish, vegetables, pastas, etc. Stays away from red meat. He started to lose weight and this has helped his self-esteem. Has matured and has had to grow up quickly. Had to do more radiation after the second surgery. Monitoring him after the radiation."
PART C: EXPERIENCE WITH VITRAKVI/LAROTRECTINIB				
9.LOCATION OF METASTATIC DISEASE IF APPLICABLE?	N/A	"Lymph nodes, both lungs."	"Lymph nodes, neck, wrapped around heart"	"Neck and thyroid."
10A. WHERE WAS THE PATIENT TESTED FOR THE NTRK GENE FUSION?	A. "My daughter was tested for NTRK at initial diagnosis at the [redacted] in September 2017."	[redacted]	"The [redacted] contacted the family and asked if they would be able to do genomic sequencing on his tumour through their [redacted]	[redacted] through the POG Program.

B. WAS IT DIFFERENT THAN THE TREATMENT CENTRE? **C. IF KNOWN, WHAT TECHNOLOGY WAS USED TO TEST THEIR CANCER FOR THE NTRK GENE FUSION?** **D. DID YOU HAVE TO TRAVEL TO GET TESTED?**			program [redacted] The Endocrinologist in Calgary received the call from [redacted] letting us know that his tumour showed as being NTRK mutated. Right around the same time, he received an email about Loxo101 from ASCO. A new lifeline opened up for him."	
	B. No	No	Yes	No
E.DID YOU HAVE TO PAY OUT OF POCKET TO GET TESTED?	C. "A biopsy of her tumour was carried out to diagnose the cancer but I don't know details."	N/A	WGS and RNA- sequencing.	
F. DID YOU HAVE TO WAIT LONG FOR THE TEST RESULTS?	D. No	"Yes, we had to travel from Michigan to Texas for testing and treatment."	"No. WE had gone to [redacted] for surgery where samples of the tumour had already been retained. We had to travel for the surgery but did not have to travel for the testing."	No
G. DID YOU EXPERIENCE ANY ANXIETY WAITING FOR THE RESULTS?	E. No	No.	No	No
	F. 3 weeks	"No, we waited less than two weeks."	A few weeks.	A few Weeks.
	G. "We tried to wait for these biopsy results before starting chemotherapy so that the treatment could be tailored to the condition but the testing **took a long time** and my daughter's condition seemed to be worsening so we went ahead and started chemo without knowing the full biopsy results. This was a worrying time."	"Yes, but I was also hopeful because we had had such bad luck so far."		
11. HOW WERE YOU ABLE TO ACCESS LAROTRECTINIB? I.E. CLINICAL TRIAL?	Clinical Trial	Clinical trial	"The Oncologist put in the application to Alberta Health to access the clinical trial in Seattle. It was initially submitted for $50,000 which would have covered the trial and tests. The family's application was denied. The Oncologist talked to the pharmaceutical company. The company said that they would pay for everything including travel and hotel for him and 2 Guardians. "	Clinical Trial in Seattle.
12.A. WHEN DID THE PATIENT FIRST RECEIVE LAROTRECTINIB (DATE)? **B. AND IN WHAT LINE OF THERAPY?** **C. HOW MANY MONTHS OR CYCLES HAS THE PATIENT BEEN ON LAROTRECTINIB?**	A. September 2018	April 5th, 2018	"July 2017. The first visit was 5 weeks long. Then, we the family went to Seattle once a month. Due to COVID-19, February was our last trip to Seattle, and everything has been done virtually since then which has been extremely beneficial. Approval was given to send the medication through the mail for him."	

	B.	Third line		Relapse Therapy.
	C. She is now on **cycle 29**	**31 months**	"The trial is 5 years in duration. He has been receiving treatment for **42 months**. He has 18 months left on the clinical trial."	**32 months on the Loxo so far**.
13. BASED ON THE THERAPIES RECEIVED PRIOR TO LAROTRECTINIB FOR METASTATIC DISEASE, HOW LONG (IN WEEKS, MONTHS, OR YEARS) DID THE PATIENT RESPOND TO EACH OF THE THERAPIES?	N/A	"**There was no response to previous treatments."**		
14.A. HAS THE PATIENT EXPERIENCED ANY SIDE EFFECTS WHILE ON LAROTRECTINIB? Y/N	A. "Yes but only minor and these have not always been easy to ascertain due to her age"	Yes.	Yes	Not really.
B. IF SO, WHAT WERE THOSE SIDE EFFECTS?	B. "Some nausea and diarrhea on starting treatment which subsided after a couple of weeks. Increase in appetite and weight gain (although in her case this was very welcome). Muscle pain and lethargy at treatment withdrawal. Neutrophil count reduced during minor infection but increased after a couple of days."	"Slight dizziness, muscle soreness and weakness."	"He has had elevated liver enzymes on and off; however, this has not required treatment to be stopped. It is important to stay on schedule. If medication is given a little late, he gets all over body aches and pains."	"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."
15. ON A SCALE OF 1-10, HOW WOULD YOU RATE THE PATIENT'S QUALITY OF LIFE WHILE ON LAROTRECTINIB? 1 BEING VERY POOR AND 10 BEING VERY GOOD. PLEASE PROVIDE ANY COMMENTS ABOUT QUALITY OF LIFE.	**10** "My daughter leads a relatively normal life for a three-year-old. She has been thriving ever since commencing Larotrectinib. She is now at nursery school and meets all of her developmental milestones. Growth has been on a smooth trajectory and her disease is very well controlled meaning that hospital admissions have been virtually non-existent."	"**Mostly 8.** "Some days 5-6. Most of the time he can do anything like normal. He runs and does weight training every day. Some days his symptoms get a little tough right before it is time to take his next dose and he needs to take it easy. Once in a great while he needs to rest for most of the day."	"Being on larotrectinib has been **like night and day**. They watched him improve daily and come back to his old self. He could breathe, his energy came back, he could eat, he gained weight."	"He doesn't like the fact that he has to take the medication, wants to be a teenager. One positive is that he doesn't drink much as he has to be responsible to take the medication. But sometimes this means that he will shelter himself and not go out. Dealing with cancer during the teenage years is very challenging – being robbed of their formative years. Doesn't like being thought of as being the kid with cancer. It is a huge difference in terms of his quality of life. He can still go out and do things. With radiation, he can't be around anyone. With Loxo, he can go out and do things and be with people. It is a huge difference. With radiation he was very sheltered, it was a psychological burden. This is not experienced with Loxo."
16. ON A SCALE OF 1-10, HOW WOULD YOU RATE YOUR	**7**	**8**		"You have to be thankful for the things you have, don't sweat the

FAMILY'S QUALITY OF LIFE WHILE ON LAROTRECTINIB? 1 BEING VERY POOR AND 10 BEING VERY GOOD. PLEASE PROVIDE ANY COMMENTS.	"She is thriving and consequently we are **much happier** as a family but the travel to access the clinical trial drug affects family life. She and I travel to London every four weeks which affects my working patterns, our other two children's routines and my daughter's education once she gets to that stage. (It is worth pointing out that we haven't travelled to London during the pandemic, which has been amazing.) My daughter spends abnormal amounts of time on her own with me and has therefore been particularly attached to me, which is understandable. This affects family life too. She has never had any normal childhood vaccinations, so we are still very careful about where we go and family activities that we agree to. Starting nursery school has been a worry but so far she has adapted well and the school is very understanding. The monthly testing causes anxiety for me, as her primary caregiver and we know that disease progression can happen quickly and dramatically, so we worry about that a lot."	"The medication really helped our quality of life as a family because before he was on it we had lot of worry and stress about whether or not he would survive. Once we knew he was responding to the drug and doing well, we could get back to a more normal routine. Prior to his being on the drug, I was also consumed with taking care of him and sometimes my other children would feel neglected. Once he started to improve, I was able to focus more of my attention on the other children."		small stuff. You can't take things for granted. Enjoy what you have around you and helping others. It has been a very difficult five years. Never thought that they would be in this predicament. You go to clinic and look around at the different families, we are really all the same in what we are experiencing. Have gone through so many different emotions but always try to keep it positive. Siblings have so many challenges also and may be treated differently than the child with cancer. Have to be positive about the future. It is emotionally draining. You see your child go through so many different challenges and sometimes you can only watch them go down the rabbit hole. You want them to be kids and have that chance at life. It is a deadly disease and scary. Focus on the times when your son is happy, healthy, and can do the things that he wants to do. You still have to be their parents and help them grow up and follow the rules. You have to put one foot in front of the other and just keep going."
17. DID THE PATIENT HAVE ANY CANCER SYMPTOMS BEFORE STARTING LAROTRECTINIB? IF SO, WHAT WERE THEY?	"No, the reoccurrence of the tumour was noticed very early on at a routine X-Ray before any symptoms had developed."	"Yes, trouble swallowing and breathing."	"Prior to larotrectinib, his colour was grey, his breathing difficult which made it an effort to get from the living room to the kitchen. He had no appetite and was wasting away."	
18. IF THE PATIENT DID HAVE CANCER SYSMPTOMS BEFORE STARTING LAROTRECTINIB, DID LAROTRECTINIB HELP RESOLVE THOSE CANCER SYMPTOMS? IF SO, WHICH ONES?		"Yes, they were all eliminated because of the Larotrectinib."	"All of the above symptoms resolved after starting larotrectinib. One side-effect of larotrectinib is weight gain, which was a welcome side-effect. He also has ADHD and has a lot of energy."	
19.A. HOW WAS RESPONSE CONFIRMED TO LAROTRECTINIB; CLINICALLY (SYMPTOMS RESOLVED), BIOCHEMICALLY, OR	"Imagining. An x-ray after two months of Larotrectinib showed significant tumour reduction and a CT scan in Jan 2019 **confirmed complete response."**	"CT Scan."	"Pre and post scans were done. In October, the scan showed a dramatic difference. They didn't really realize how sick he was until they started to	

RADIOGRAPHICALLY (SUCH AS THROUGH CT)? **B. WHAT WAS THE RESPONSE TO LAROTRECTINIB?**			see him improve and how much of a difference larotrectinib had on his life. Larotrectinib is taken x2 daily."	
	B. "My daughter experienced **complete response** for 12 months before stopping Larotrectinib in Jan 2020 to see what would happen. Unfortunately, after two months, a CT scan showed some tumour regrowth at the original site. She immediately restarted Larotrectinib and achieved **complete response again by May 2020**. This has been maintained to date."	"**COMPLETE RESPONSE."**	Huge difference.	
20. DID THE PATIENT EVER HAVE TO STOP LAROTRECTINIB? WHY? WHAT HAPPENED WHEN THEY STOPPED TAKING LAROTRECTINIB?	"Larotrectinib was stopped in Jan 2020 after one year of remission. We stopped because we wanted to know if she could maintain remission without the drug. This was not possible and the tumour returned after 2 months without the drug."	No.	No	
21. HAS LAROTRECTINIB BEEN EASIER TO USE THAN PREVIOUS THERAPIES? WHY OR WHY NOT?	"Very much so! She only takes a small oral dose twice a day which is easy to manage and the side effects are so minimal compared to chemotherapy."	"Yes. It is much more tolerable than surgeries and radioactive iodine."	Yes	Yes
22. WAS IT WORTH ACCESSING LAROTRECTINIB? WHY OR WHY NOT?	"Absolutely. This drug saved our daughter's life after conventional chemotherapy and surgery failed to deal with the tumour in her lung and it has also given her amazing quality of life."	"Yes. It was the only thing that worked to reduce the metastatic tumours."	"Yes. Didn't think about what phase of trial it was, it was his only option. The family did their research and heard positive stories about larotrectinib working for others. It was enough to give us a leap of faith. We might not have pursued a phase ½ clinical trial if there were other options, but we had looked all over for these options and they were not available to him.".	Yes
23. DID ACCESSING LAROTRECTINIB ALLOW THE PATIENT TO FULFILL OR ACCOMPLISH ANYTHING THAT THEY WOULD NOT HAVE OTHERWISE BEEN ABLE TO DO HAD THEY NOT ACCESSED THE THERAPY? IF YES, PLEASE EXPLAIN.	"Yes! My daughter now leads a life which is comparable to her peers. She is thriving. She is an adored little sister and cousin, with lots of friends. None of this would have been possible without Larotrectinib."	"Yes. This medication saved my son's life. Without it he would not be here. He is fifteen so it has allowed him to start high school and make friends and live as a normal teenager. Without it, he would not be alive."	"He is now 11 years old and is in grade 6"	"Past three years have been a huge difference. Now has a small circle of friends. Has a job, has his own car and drives, now more social, will go out with his friends. He has become much more social. Has been making lots of changes and has matured. This has helped a great deal with not being in hospital."
24. WHAT IMPROVEMENTS WOULD YOU LIKE TO SEE IN A DRUG THERAPY THAT IS NOT AVAILABLE IN CURRENTLY AVAILABLE THERAPIES?	"The conventional chemotherapy treatments which she tried were extremely hard on her body and were ultimately unsuccessful. She could not lead a normal life	"More research into the long-term effects of ongoing use of targeted chemotherapy and Oncogene drugs. Fewer side effects if possible,		

	during chemotherapy, and neither could we as her family. “	through the side effects are tolerable.”		
25. WOULD YOUR CHILD’S LIFE BE ANY DIFFERENT IF THE DRUG THERAPIES HAD THOSE DESIRED IMPROVEMENTS?	“As a family, it felt like we were holding our breath for the months of conventional chemotherapy and surgical treatments that my daughter endured. We watched her fail to thrive and we had no control over our day-to-day lives as we would often have to drop everything for another hospital admission. This was very hard on our other two children. With kinder, more targeted cancer treatments and therefore better quality of life for cancer patients, the whole would be positively affected.”	“We would know when it was best to go off-and-on the drug, and no side effects would be ideal.”		“Doesn’t matter where you have to go, would go to the moon and back if it means finding the right treatment for your child. Quality of life, how he feels and how he adapts to it. It is all about him. All about his wellbeing. It is about his life, longevity. If there was that magic tablet in the sky, we would sell everything and go get it. It is all about hope and faith. Those decisions are hard to make as a teenager.”
26. DO YOU BELIEVE LAROTRECTINIB HAS THOSE DESIRED IMPROVEMENTS? WHY OR WHY NOT?	“Unlike the chemotherapy treatments we experienced, this drug has enabled her (and consequently the rest of the family) to lead a relatively normal life, whilst controlling her disease very effectively. This has been revolutionary for us.”	“Larotrectinib is extremely tolerable but because it is new, the rest of the things we would like to understand will take time to get a clear picture.”		
27. DO YOU WISH TO ADD ANYTHING ABOUT WHY ACCESSING LAROTRECTINIB IS SO IMPORTANT TO PATIENTS AND CAREGIVERS?	“We cannot stress enough how grateful we are for this treatment, for my daughter especially, but also for the rest of our family who endured months of grueling chemotherapy regimens which were ultimately ineffective in dealing with the cancer. We hope that families around the world can have the experience of accessing this drug without having to meet drug trial requirements and without first having to try conventional chemotherapy treatments. The speed with which Larotrectinib deals with the cancer and minimal nature of the side effects we have observed are astounding.”	“Larotrectinib literally saved my son’s life. We were completely out of options and had to move heaven and earth to find a doctor who might be able to help. When he started on this trial, and it worked, after years of disappointment, it felt like a miracle. Access to this medication is absolutely essential for kids who have NTRK positive tumours. It is my belief that this could be extremely helpful as a first line treatment even before surgery in some cases.”		“The team in Vancouver is amazing. Communication between the two hospitals has been seamless. They are very patient friendly. Feel very fortunate to be in this study. It has helped the family so much. It has been a good experience for sure. Amazing that the two countries can work together. The team in Seattle has been very good as well. [redacted]. Have not met any other families with the same diagnosis. Always looking around to see if other kids have the same type of cancer.”

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Larotrectinib for the Treatment of Adult and Pediatric TRK Gene Fusion Positive Cancers**
Name of the Patient Group	**Colorectal Cancer Canada**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

Colorectal Cancer Canada is registered with CADTH.

www.colorectalcancercanada.com

2. Information Gathering

To help capture the patient perspective on this disease site-agnostic cancer therapy under review, Colorectal Cancer Canada launched an online patient/caregiver survey from October 30, 2020 to November 30, 2020 of which 6 patients and 5 caregivers (Patient 1-6, Caregiver 1-5) responded. Data was gathered from patients across Canada, the United States, and Brazil. The survey was posted on CCC's social media platforms as well as on an online NTRK support group in the U.S in order to reach out to as many patients and caregivers as possible. Three CCC representatives also participated in an international NTRK conference meeting with NTRK patients and their caregivers. This conference helped CCC better understand the patient perspectives and enabled CCC to interact with NTRK-positive patients undergoing treatment with Larotrectinib. Additionally, in June 2020 CCC had reached out to two patients (Patient 7 and Patient 8) to provide their experiences with the therapy under review by participating two-hour long telephone interviews. Previously, at ASCO 2018, a CCC representative met with over 20 patients and

caregivers and remained in touch with three patients to monitor their progress over the course of the past two years. As a result of this outreach, CCC spoke to eight patients and five caregivers in total who provided detailed and high quality responses to our questions:

- 4 Thyroid Cancer Patients (Patient 3, 6, 8 and Caregiver 3)
- 2 Lung Cancer Patients (Patient 1 and 2)
- 2 Salivary Gland Cancer Patients (Patient 7 and Caregiver 5)
- 2 Sarcoma Cancer Patients (Caregiver 2 and 4)
- 1 Colorectal Cancer Patient (Caregiver 1)
- 1 Pancreas Cancer Patient (Patient 4)
- 1 Neuroendocrine Cancer Patient (Patient 5)

The qualitative data on patient demographics is summarized and represented in Table 1 (patients) and Table 2 (Caregivers), and will serve as the basis for this qualitative submission.

Table 1: Surveyed and Telephone Interviewed Patients – Information Gathering

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Connection to Cancer	Patient undergoing Tx	Patient undergoing Tx	Patient undergoing Tx	Patient undergoing Tx	Patient undergoing Tx	Patient undergoing Tx	Patient undergoing Tx	Patient undergoing Tx
Country and Region	Brazil / São Paulo	Canada/Ontario	Canada/British Columbia	United States	United States	United States	United States/Oklahoma	United States/Louisiana
A. Gender B. Age at Dx	A. Female B. 40-49 years	A. Male B. 50-59 years	A. Female B. 30-39 years	A. Female B. 60-69 years	A. Male B. 60-69 years	A. Female B. 30-39 years	A. Male B. 50-59 years	A. Female B. 30-39 years
A. Cancer Type B. Date of Dx	A. Lung B. 27/08/2018	A. Lung B. 11/2013	A. Thyroid B. 06/1998	A. pancreas B. 06/08/2018	A. Neuroendocrine midgut B. 28/10/2018	A.Thyroid B. 2004	A. Salivary Gland B. 10/2014	A. Papillary Thyroid Cancer B. 01/2003

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
A. Stage at Dx B.Metastases	A. Stage IV B. Peritoneum	A. Stage IV B. Brain/CNS, liver, bones	A. Stage I B. Lung	A. Stage IV B. Lung, Lymphatic system, liver	A. Stage IV B. Liver, Omentum, abdominal caking	A. Stage I B. Brain/CNS, lung, thyroid	A. Stage IV B. lungs, liver, kidneys and multiple lymph nodes	A. Stage IV B. Brain/CNS, Lungs, jaw muscle, liver, gallblader, lymph nodes in neck, lymph nodes in right armpit

Table 2: Surveyed Caregivers – Information Gathering

	Caregiver 1	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
Connection to Cancer	Caregiver on behalf of patient undergoing treatment	Caregiver on behalf of patient previously treated	Caregiver on behalf of patient undergoing treatment	Caregiver on behalf of patient undergoing treatment	Caregiver on behalf of patient undergoing treatment
Country and Region	United States/Indiana	United States	Canada/Alberta	United States/New Jersey	Canada
A. Gender B. Age at Dx	A. Male B. 50-59 years	A. Female B. 10-19 years	A. Male B. 0-9 years	A. Female B. 0-9 years	A. Female B. 30-39 years
A. Cancer Type B. Date of Dx	A. Colorectal B. 8/03/2019	A. Sarcoma B. 22/10/2019	A. Thyroid B. 09/2014	A. Infantile Fibrosarcoma B. 09/2018	A. Salivary gland B. 02/2008
A. Stage at Dx B. Metastases	A. Stage IV B. N/A	A. Stage 0 B. None	A. Stage IV B. Lung	A. I don't know B. None	A. Stage IV B. lymph nodes in neck

3. Disease Experience

Patients and caregivers were asked if any cancer-induced symptoms were experienced prior to diagnosis. Eight out of thirteen patients (62%) had experienced symptoms and those varied from fatigue, cough, abdominal/back pain as well as body lumps. Six out of thirteen patients (46%) said that pain is the symptom that is more important to control than others. Other patients said fatigue and shortness of breath were symptoms that are more important. Aside from patient 1 who feels symptoms are bearable, all other patients feel that their symptoms affect their daily life. Patient 2, 4, 5 and 8 felt symptoms affected their work-life and daily activities. For instance, patient 8 mentioned: "*I had to stop driving because of pain in my leg".* Additionally, symptoms had a psychological impact on 5/12 patients (42%) including mental health issues such as anxiety and depression.

Caregivers were uniquely questioned on the difficulties faced while caring for the patients. Two out of five caregivers (40%) mentioned that the impact of the disease on them became tolerable only when Larotrectinib was administered: *"with larotrectinib the side effects and treatment were amazingly 'simple' than traditional chemo and radiation"* (Caregiver 2), and *"before Vitrakvi my husband needed me at home … This drug has given us back hope and a 'return-to normal' for him".*

The qualitative data on disease experience is summarized and represented in Table 3 (patients) and Table 4 (caregivers).

Table 3: Surveyed and Telephone Interviewed Patients – Disease Experience

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Symptoms experienced from cancer prior to Dx	Yes, cough	Yes, lower back pain	No	Yes, sharp pain in stomach	Yes, abdominal pain, cramping, headache, dizziness fatigue	No	Yes, fatigue, tumour induced pain, vomiting, fecal incontinence	Yes, small bump on upper part of leg, knot on calf muscle
Which symptoms of cancer were/are more important to control than others?	Fatigue and pain	Mobility, shortness of breath	.	Weight gain, daily withdrawal pain	Abdominal pain, headache, loss of appetite	Pain, fatigue	.	.
How symptoms and problems resulting from any symptoms impact	The symptoms limit my life little because	No to work, no to help around house, no to driving.	.	Can't work hard to exercise	Not able to work, crutches	None except withdrawal pain	.	I had to stop driving because

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
or limit quality of life	they are bearable.	Problems dressing myself and general duties around the house.			most of the time,			of pain in my leg
Psychological impact as a result of your cancer on you or your family?	It´s not a problem for me because I always believed that it was not over.	Cognitive dysfunction, short term memory loss. Depression and anxiety.	.	None	Crutches, 1 year survival rate of 14 to 44 %	Stress	.	.
On a scale of 1-10, how important to you is the access to new effective treatments for cancer, with 1 being "not important" and 10 being "very important"?	Very important10	Very important10	Very important10	Very important10	Very important10	Very important10		

Table 4: Surveyed Caregivers – Disease Experience

	Caregiver 1	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
Symptoms experienced from cancer prior to Dx	No	No	No	Yes, Mass on forearm	Yes, Original cancer- a hard, painful lump behind the ear. Current cancer- back and stomach pain, loss of appetite, shortness of breath, whisper-like voice.
Which symptoms of cancer were/are more important to control than others?	.	.	Pain,mobility, shortness of breath	Movement in hand	Pain, 100 per cent. Shortness of breath comes second.
How symptoms and problems resulting from any symptoms impact or limit quality of life	.	.	.	Infant N/A	.
Psychological impact as a result of your cancer on you or your family?	.	.	.	.	I have noticed increased anger in my spouse. My mental health has suffered for sure and so has our daughter's. She is improving seeing her dad working and looking 'normal' again.
Difficulties caregiver faced:	No Difficulties	Yes, having a child with cancer and seeing the him go through that experience…but with Larotrectinib the side effects and treatment were amazingly 'simple' than traditional chemo and radiation. Also having another child and the struggles he	Yes, loss of income	Yes,	Yes, before Vitrakvi my husband needed me at home to help with draining his lung catheter, looking after his meds, preparing meals, grooming, etc. It was taxing at times. It's also been hard emotionally. This drug has given us back hope and a 'return-to normal' for him. He is leading a productive life because of the reduced or minimal side effects and the drugs' success (in terms of tumour shrinkage). That has allowed me to

	Caregiver 1	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
		went through during his brother's treatment. The financial cost would have been near impossible if we were not in a trail study for this medicine.			breath easier knowing he is doing so well.

4. Experiences With Currently Available Treatments

Ten out of thirteen (77%) patients accessed previous therapies for the treatment of their respective cancers as seen in Table 5 and 6. Therapies included chemotherapy, radiation therapy and surgery. Patients that were telephone interviewed received radiotherapy (Patient 7 and 8) and surgery (patient 7). Patients were questioned what side effects were most difficult to tolerate from their therapies and responses varied from pain to nausea, fatigue and diarrhea. Patients reinforced that if they had a choice of drugs to treat their cancer, it is "very important" for them to make a choice based upon each different drug's known side effects. In addition to treatment cost, more than half of previously-treated patients (63%) noted travel as an additional expense incurred by accessing their treatments. Patients also experienced other difficulties in accessing drugs for their cancers such as Caregiver 3 who noted that their drugs were not approved or funded for in Canada, which led them to move to the United States for a clinical trial to get treatment. Paying out of pocket to access new drug therapies is controversial to patients: some would be willing to *"do whatever it takes"* (Caregiver 4) , while for some that would require them to *"sell their home"* (Caregiver 5), or even *"end up bankrupt"* (Patient 3).

The qualitative data on patients' experiences with currently available treatments is summarized and represented in Table 5 (patients) and Table 6 (caregivers). Patients 7 and 8 did not answer detailed questions related to previous therapies and are therefore excluded from the table.

Table 5: Surveyed and Telephone Interviewed Patients – Experiences With Currently Available Treatments

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
If Larotrectinib is not your first line treatment, what treatments have you received previously?	Chemotherapy, Radiation therapy	Chemotherapy, Radiation therapy	No other treatment	Chemotherapy, Radiation therapy	Chemotherapy	Radiation therapy, surgery
Have these therapies been effective at controlling the symptoms resulting from your cancer?	No	Yes	.	Partially	Partially	Partially
What side effects have you experienced with your previous treatments?	Fatigue	Hair loss, fatigue, pain	.	Diarrhea, nausea, hair loss, vomiting, fatigue	Nausea, hair loss, fatigue, vomiting, anemia, low white blood cell count, fatigue, infections	Low white blood cell count, pain, hormonal changes
Top two side effects that were most difficult to tolerate:	.	.	.	Pain from tumor, nausea	Nausea, fatigue	.
Have you (or your oncologist) experienced any difficulties in accessing drugs for your cancer?	No	No	.	No	No	No
Were any of your treatments recommended solely	No	I don't know	.	No	No	I don't know

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
based on what was funded in your region of residence?						
Have you had to pay out of pocket for any of your previous treatments?	Yes	No	.	No	No	Yes
Did you receive any financial assistance from a pharmaceutical/biotech company assistance program or any other assistance program? If yes, what percentage of the total cost of the treatment was provided?	Yes, 100%	No	.	Yes, 100%	Yes, 0.5%	No
In addition to the treatment cost, were there other costs incurred by you in accessing the treatment, such as travel costs, drug administration, etc.?	Yes, Travel costs and drug administration.	No	.	No	Yes, Travel, loss of income from loss of job	Yes, Car, tolls, parking
Would you be willing to pay out of pocket to access new drug therapies for the treatment of your cancer in a private clinic?	No, Because I don´t have money for it.	No, I cannot afford any.	Depends on the cost, I will end up bankrupt while trying to control my metastatic cancer.	Depends on the cost	Yes	Depends on the cost, $30k/month is not accessible

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
On a scale of 1-10, with 1 being "not important" and 10 being "very important", if you had had a choice of drugs to treat your cancer, how important was it for you to make that choice based upon each different drug's known side effects?	Very important10	Not important 1	Very important10	Very important10	Very important10	9

Table 6: Surveyed Caregivers – Experiences With Currently Available Treatments

	Caregiver 1	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
If Larotrectinib is not your first line treatment, what treatments have you received previously?	Chemotherapy , Surgery	No other treatment	Radiation therapy, surgery	No other treatment	Chemotherapy, radiation therapy, surgery
Have these therapies been effective at controlling the symptoms resulting from your cancer?	Yes	.	Partially	.	Partially
What side effects have you experienced with your previous treatments?	Diarrhea, nausea, hair loss, fatigue, hand and food syndrome	.	fatigue	.	Diarrhea, nausea, hair loss, mouth sores, fatigue, pain, skin rash, sore muscles and joints, loss of taste, reduced saliva, burned skin
Top two side effects that were most difficult to tolerate:	.	.	.	.	Sore, achy joints and diarrhea
Have you (or your oncologist) experienced any difficulties in accessing drugs for your cancer?	No	.	Yes, Not approved / funded in Canada. Had to go to a trial	.	No

	Caregiver 1	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
			in the USA to get treatment		
Were any of your treatments recommended solely based on what was funded in your region of residence?	I don't know	.	N/A	.	No
Have you had to pay out of pocket for any of your previous treatments?	No	.	No	.	No
Did you receive any financial assistance from a pharmaceutical/biotech company assistance program or any other assistance program? If yes, what percentage of the total cost of the treatment was provided?	Yes	.	Yes, 100%	.	.
In addition to the treatment cost, were there other costs incurred by you in accessing the treatment, such as travel costs, drug administration, etc.?	Yes	.	Yes, some travel expenses	.	Yes, Travel to hospital five hours away.
Would you be willing to pay out of pocket to access new drug therapies for the treatment of your cancer in a private clinic?	Yes	Yes	Yes, medicine works very well	Yes, If my child's life depended on it I would do whatever it takes	Depends on the cost, Currently we would have to sell our home to pay for any future drug costs not covered under our medical plan.
On a scale of 1-10, with 1 being "not important" and 10 being "very important", if you had had a choice of drugs to treat your cancer, how important was it for you to make that choice based upon each different drug's known side effects?	Very important10	Very important10	9	Very important10	7

5. Improved Outcomes

All patients and caregivers (100%) expressed a common reaction regarding new therapies: the increased importance for new therapies to bring about improvement in their physical condition and quality of life. Trade-offs commonly considered when choosing therapy include both extended overall survival and quality of life. Caregiver 4 and Patient 4 would be willing to tolerate significant side effects in order to extend survival by 1 year. But also, nine out of eleven (82%) would be willing to take a drug that provides better quality of life even if it doesn't extend overall survival. They feel the need to be able to carry on normal activities and be socially engaged without the burden of the therapies side effects that aggravate their quality of life. Lastly, Patient 1 (Brazil) and Patient 3 (Canada) say that access to drug therapies in their respective countries is limited/restrictive, while Patient 2 (Canada), 5 (U.S) and Caregiver 4 (U.S) say that access to drug therapies in their respective countries is appropriate/fair.

The qualitative data on improved outcomes is summarized and represented in Table 7 (patients) and Table 8 (caregivers). Telephone interviewed patients were not asked these specific questions.

Table 7: Surveyed and Telephone Interviewed Patients – Improved Outcomes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
On a scale of 1-10, with 1 being "not important" and 10 being "very important", if you were to consider taking a new therapy for your cancer, how important is it for you that:						
New therapies bring about improvement in your physical condition?	Very important 10	Very important 10	Very important 10	Very important 10	Very important 10	Very important 10
New therapies bring about improvement in your quality of life?	Very important 10	Very important 10	Very important 10	Very important 10	Very important 10	Very important 10
You understand the average (or median) period of expected benefit from that new therapy?	Not important 1	5	Very important 10	Very important 10	Very important 10	9
Would you take a drug that has been proven to provide better Quality of Life during your lifetime even if it does not extend overall survival?	Yes	Yes	No	Yes	Yes	Yes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
On a scale of 1-10, with 1 being "no side effects" and 10 being "significant side effects", if you were to consider taking a new therapy for your cancer, what severity of side effects are you willing to tolerate in order to extend survival by:						
(a) 2 months?	no side effects1	no side effects1	5	6	5	no side effects1
(b) 6 months?	3	no side effects1	5	8	6	3
(c) 1 year?	8	4	5	significant side effects10	7	5
On a scale of 1-10, with 1 being "not important as long as there is a drug" and 10 being "very important to choose which drug would be best suited for me", if you were to consider taking a new therapy for your cancer, how important is it for you and your physician to have a choice in deciding which drug to take?	very important 10	very important 10	very important 10	very important 10	very important 10	very important 10
On a scale of 1-10, with 1 being "very limited/restrictive" and 10 being "very appropriate/fair", to ensure the best outcome for your cancer, would you say that access to drug therapies in your province (state)/country is limited/restrictive or is it appropriate/fair?	very limited/restrictive1	very appropriate/fair10	very limited/restrictive1	8	very appropriate/fair10	5
On a scale of 1-10, with 1 being "not important" and 10 being "very important", if your government or funder (such as insurance company, hospital or other funder) was to fund a minimum of two therapies for the treatment of your cancer, how important is it for you that your	Very important 10	Very important 10	Very important 10	Very important 10	Very important 10	Very important 10

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
oncologist have flexibility in deciding which of those therapies to choose?						

Table 8: Surveyed Caregivers – Improved Outcomes

	Caregiver 1	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
On a scale of 1-10, with 1 being "not important" and 10 being "very important", if you were to consider taking a new therapy for your cancer, how important is it for you that:					
New therapies bring about improvement in your physical condition?	Very important 10	Very important 10	Very important 10	Very important 10	Very important 10
New therapies bring about improvement in your quality of life? For example: Improved mobility, sense of wellness, relief from side effects?	Very important 10	Very important 10	Very important 10	Very important 10	Very important 10
You understand the average (or median) period of expected benefit from that new therapy?	Not important 1	Very important 10	7	8	5
Would you take a drug that has been proven to provide better Quality of Life during your lifetime even if it does not extend overall survival?	No	Yes	Yes	Yes	Yes
On a scale of 1-10, with 1 being "no side effects" and 10 being "significant side effects", if you were to consider taking a new therapy for your cancer, what severity of side effects are you willing to tolerate in order to extend survival by:					
(d) 2 months?	N/A	2	4	4	2
(e) 6 months?	N/A	4	5	7	3
(f) 1 year?	N/A	4	7	significant side effects10	4
On a scale of 1-10, with 1 being "not important as long as there is a drug" and 10 being "very important to choose which drug would be best suited for me", if you were to	N/A	very important 10	very important 10	very important 10	7

	Caregiver 1	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
consider taking a new therapy for your cancer, how important is it for you and your physician to have a choice in deciding which drug to take?					
On a scale of 1-10, with 1 being "very limited/restrictive" and 10 being "very appropriate/fair", to ensure the best outcome for your cancer, would you say that access to drug therapies in your province (state)/country is limited/restrictive or is it appropriate/fair?	N/A	9	3	very appropriate/fair10	7
On a scale of 1-10, with 1 being "not important" and 10 being "very important", if your government or funder (such as insurance company, hospital or other funder) was to fund a minimum of two therapies for the treatment of your cancer, how important is it for you that your oncologist have flexibility in deciding which of those therapies to choose?	N/A	Very important 10	9	Very important 10	Very important 10

6. Experience With Drug Under Review

As evidenced in Tables 9-11, six out of thirteen (46%) patients had access to the drug under review via clinical trials, while others had access to the drug through special access programs, scholarships, and insurance plans. Most had no financial restrictions when accessing the drug; however, Caregiver 3 reported that "*the drug was not available in [the] cancer center/hospital, [did not have] access to a clinical trial, [had] no provincial coverage, [and therefore had] travel costs associated with accessing therapy."*

All patients were prescribed Larotrectinib after being tested positive for the NTRK gene, but in different lines of therapy (first line to fifth line). Patient 6 changed treatment options to Larotrectinib as third line therapy only after *"finally [having] genomic testing"*. When asked about a particular gap or unmet patient need with current therapies, most patients emphasized the importance of having a drug that targets a cancer mutation, and the particular need for increased molecular profiling. Most importantly, patients and caregivers rated side effects' impact on daily living as very low (1-4) on a scale from 1-10, and considered them tolerable and relatively minor. While most faced no particular issues while taking this drug, others experienced some fatigue, anxiety, pain and long hours spent in medical appointments. Particularly, Caregiver 2, 3 and 5 felt the most difficult aspect of Larotrectinib were monetary concerns: *"The worry that it won't be covered by our private insurance or our government insurance. If the tumours are inoperable and the other therapies won't work, the worry that Vitrakvi will not be available in Canada is very difficult"* (Caregiver 5).

When questioned what effect patients expect, or hope, that Larotrectinib will have on the cancer and their prognoses, 90% of caregivers and patients reported "maintaining and improving quality of life", and currently while on the drug, they all rate their quality of life as "high or normal living". They were also asked if the drug under review allowed them to fulfill or accomplish anything that they would not have otherwise been able to, had they not accessed the therapy. Patients voiced a common answer that the drug allowed them to resume all their daily activities: "*a productive and 'normal' life. He would not be living the same way on chemotherapy or with radiation treatments"* (Caregiver 5); *"To be able to have a 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"* (Patient 7).

Patients and caregivers mentioned that there are no symptoms that Larotrectinib manages less effectively than the existing therapies. According to patients, the drug under review does manage certain symptoms better than existing therapies including: nausea, vomiting, pain, fatigue, and dizziness. Above all, 100% of patients and caregivers following treatment have their tumour completely gone, shrunk or controlled, and most importantly live a high quality of life with minimal side effects. Additionally, all patients appreciate the easily administered oral therapy and find it simple to integrate in their daily routine. Compared to other treatments, all patients and caregivers rated their overall experience with the drug under review between an 8 and 10 on a scale of 1-10.
All patients and caregivers (100%) responded yes when asked if they believe the drug under review should be funded where they reside for the treatment of cancer: *"Yes, it was our 'miracle' drug"* (Caregiver 5).

The qualitative data on the experience with drug under review is summarized and represented in Table 9 (survey patients), Table 10 (telephoned patients) and Table 11 (Caregivers). For this section, Caregiver 1 did not respond to any of the questions and is therefore not shown in the table.

Table 9: Surveyed Patients – Experience with Drug under Review

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
At the start of your discussion with your oncologist, were you informed of Larotrectinib (VITRAKVI) by your oncologist as a potential treatment option for you?	Yes	No	No	No	No	Yes
Why were you prescribed Larotrectinib (VITRAKVI)?	Because I have an NTRK1 gene mutation and it was the only drug that could help me.	My gene mutation matched.	Dec., 2019 Foundation One Medicine said lung biopsy positive for NTRK3 - ETV6	Acinar cell pancreatic cancer	NTRK fusions positive cancer	NTRK positive cancer
In what line of therapy were you prescribed/given Larotrectinib (VITRAKVI) for the	First Line	Fourth Line	First Line	fifth line	Second Line	Third Line

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
treatment of your cancer?						
Did you participate in a clinical trial in connection to this drug? If yes, please specify clinical trial name and location:	Yes, Portugal - Porto	No	No	No	No	yes, Philadelphia, Pennsylvania
How long have you been taking Larotrectinib (VITRAKVI)? Please specify below:	one year and three months	20 months		Four months	18 months	26 months
If applicable, did you change your treatment option to Larotrectinib (VITRAKVI) after recurrence*? If yes, why?	No	No	N/A	No	No	Yes, Finally had genomic testing
In your opinion, is there a particular gap or unmet patient need with current therapies that Larotrectinib (VITRAKVI) will help alleviate?	No	No	Yes, Larotrectinib targets my ntrk gene fusion specifically.	Yes, All new patients should have ngs testing on their solid tumor mass	Yes	Yes, Quick tumor shrinkage, minimal side effects

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
What effect do you expect (or hope) that Larotrectinib (VITRAKVI) will have on the cancer and your prognosis?	Maintain or improve quality of life	Maintain or improve quality of life, Increase overall survival, Delay onset of symptoms, q Ease of use	Maintain or improve quality of life, Increase overall survival, Delay onset of symptoms, Delay need for chemotherapy, Ease of use	Maintain or improve quality of life, Increase overall survival	Maintain or improve quality of life, Increase overall survival, Delay onset of symptoms, Delay need for chemotherapy, Reduce side effects from current medications or treatments, Ease of use	Maintain or improve quality of life, Increase overall survival, Delay onset of symptoms, Delay need for chemotherapy, Reduce side effects from current medications or treatments, Ease of use
Which symptoms does Larotrectinib (VITRAKVI) manage better than the existing therapies?	nausea, vomiting, malaise	Overall great feeling knowing cancer is stable	N/A - Larotrectinib is my 1st line of treatment.	Nausea	Pain, nausea, fatigue, headache, dizziness	Shrunk tumors in lungs
Which symptoms does Larotrectinib (VITRAKVI) manage less effectively than the existing therapies? Please describe below.	I don´t know	None	N/A - Larotrectinib is my 1st line of treatment.	Daily Withdrawal pain in between doses	None	
Was Larotrectinib (VITRAKVI) able to	Yes	Yes	Yes	Yes	Yes	Yes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
shrink/control your cancer and/or spread of the disease to other organs (metastases)?						
What side effects have you experienced while on Larotrectinib (VITRAKVI)?	Tiredness, nausea, constipation, decreased appetite, joint pain/muscle pain	Tiredness, Dizziness	Tiredness, cough, weight gain	Cough, Dizziness, Swelling of ankles/feet/hands, joint pain/muscle pain, weight gain	Tiredness, dizziness, Swelling of ankles/feet/hands, Joint pain/muscle pain, weight gain	constipation, joint pain/muscle pain, weight gain, mild facial tingling
Of the side effects experienced with Larotrectinib (VITRAKVI), which ones were most difficult to tolerate? Please identify your top three.	Tiredness, joint pains, muscle pain and vomiting	Dizziness - not sure if it has caused any dizziness Had before start from brain radiation	N/A - side effects have been very few.	Pain, weight gain	None	Muscle pain, weight gain,
On a scale of 1-10, with 1 being "no side effects at all" and 10 being "debilitating side effects that impact daily living", how would you rate your side effects while	3	3	2	2	4	3

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
taking Larotrectinib (VITRAKVI)?						
Did you have to stop the Larotrectinib (VITRAKVI) earlier than planned or did you have to skip doses due to side effects?	No	No	Yes	No	No	No
As an oral therapy (drug administered through your mouth), has Larotrectinib (VITRAKVI) been easy to administer/receive?	Yes	Yes	Yes	Yes	Yes	Yes
On a scale of 1-10, with 1 being "low/severely impacted", and 10 being "high/normal living", how do you rate your quality of life while taking Larotrectinib (VITRAKVI)?	8	8	high/normal living10	9	7	9
Were you able to continue your daily activities or work while undergoing/after	Yes	No	Yes	Yes	Yes	Yes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
completing Larotrectinib (VITRAKVI)?						
Do you find Larotrectinib (VITRAKVI) to be easy to integrate in your daily routine?	Yes	Yes	Yes	Yes	Yes	Yes
What is/are the most difficult aspect(s) of Larotrectinib (VITRAKVI) for you? Check all that apply.	No particular issues	fatigue, anxiety/worrying	No particular issues	Pain	No particular issues	Management of side effects, hours spent in medical appointments
Do you believe Larotrectinib (VITRAKVI) will change your long-term health and well-being for the better?	Yes	Yes	Yes	Yes, my tumours are gone now	Yes, It is hopefully blocking the cause of my cancer, decreasing the rate of growth and rate of new mutations that will make it stop working and hopefully turn my cancer from "uniformly having a dismal prognosis" to being a chronic disease that I can live with.	Yes avoid other harmful treatments

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Based on any experience you have had taking other drugs for your cancer: On a scale of 1-10, with 1 being "much worse" and 10 being "much better", how would you rate your overall experience with Larotrectinib (VITRAKVI) compared to other treatments?	8	much better10	N/A	much better10	much better10	much better10
Did accessing Larotrectinib (VITRAKVI) 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.	No	Mobility improvement	Yes, disease did shrink with really no terrible side effects. No other treatment available for my NTRK gene fusion.	I went white water river rafting and wading, thigh high, in a trout stream. I couldn't have done that before Vitrakvi	Yes, live life. I was constantly sick before, now I'm able to do much more like travel, garden, visit with family and friends, and make bread.	I could have easily been going down the path of having affected breathing issues since the tumors were on my bronchi but taking larotrectinib I was able to avoid this
Is Larotrectinib (VITRAKVI) approved where you reside?	Yes	I don't know	No		Yes	Yes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
How was Larotrectinib (VITRAKVI) funded for you?	Clinical trial	Special Access program	Accessed through 'compassionate use'.	Scholarships through Bayer and Longs	Insurance Plan	Clinical Trial
Do you believe Larotrectinib (VITRAKVI) should be funded where you reside for the treatment of cancer? Why or why not.	Yes, because it is very expensive.	Yes, If it saves lives it should be available	Yes, for those of us with this RARE cancer, it is a very expensive drug.	Yes	Yes, It is treating the cause of my cancer, not just poisoning my whole body trying to slow the growth of the cancer.	Yes, Void other costly procedures and/or treatments
Did you experience any financial constraints due to Larotrectinib (VITRAKVI)?	No	No	Yes	No	No	No
Have you had issues accessing Larotrectinib (VITRAKVI)? If so, what issues have you experienced?	I haven't had any issues accessing therapy	I haven't had any issues accessing therapy	Not available in my cancer center/hospital, "Did not have access to a clinical trial", no provincial coverage	I haven't had any issues accessing therapy	I haven't had any issues accessing therapy	I haven't had any issues accessing therapy

Table 10: Telephone Interviewed Patients – Experience with Drug Under Review

	Patient 7	Patient 8
Why were you prescribed Larotrectinib (VITRAKVI)?	NTRK3 Gene Fusion Positive following NGS on viable tumour sample	NTRK3 Gene Fusion Positive following NGS on lymph node from back of neck
In what line of therapy were you prescribed/given Larotrectinib (VITRAKVI) for the treatment of your cancer?	first systematic therapy	first line therapy
Did you participate in a clinical trial in connection to this drug? If yes, please specify clinical trial name and location:	Yes, LOXO 101	.
Which symptoms does Larotrectinib (VITRAKVI) manage better than the existing therapies?	pain, fatigue, incontinence, shrunk tumours	lung weaziness
What side effects have you experienced while on Larotrectinib (VITRAKVI)?	withdrawal-like symptoms such as leg cramping and tightness in my chest if I don't take the drug on time, then I am back to normal and symptoms subside	I have very few to no side effects. Sometimes I get a jittery feeling of over-stimulation 45 minutes after 1 dose, 4 hours later it's completely gone. 10 days in my therapy I had a skin sensitivity issue, but that lasted one week. Both side effects have resolved completely
Did you have to stop the Larotrectinib (VITRAKVI) earlier	"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

	Patient 7	Patient 8
than planned or did you have to skip doses due to side effects?		
On a scale of 1-10, with 1 being "low/severely impacted", and 10 being "high/normal living", how do you rate your quality of life while taking Larotrectinib (VITRAKVI)?	10	10
Did accessing Larotrectinib (VITRAKVI) 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.	"Yes, for sure. To be able to have a 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."	Yes I am working full time have my 2 cats and dog and enjoying life! Ironically because of the drug cancer is a small part of my life. It has allowed me to do. I can focus on everything else other than my cancer I feel normal!

Table 11: Surveyed Caregivers – Experience with Drug under Review

	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
At the start of your discussion with your oncologist, were you informed of Larotrectinib (VITRAKVI) by your oncologist as a potential treatment option for you?	Yes	No	Yes	Yes
Why were you prescribed Larotrectinib (VITRAKVI)?	He had the NTRK gene	Patient had A NTRK fusion. Radiation was no longer working	Infantile Fibrosarcoma	Because he has metastatic cancer, his tumours are inoperable, he has already had surgery, chemo therapy and radiation, and the cancer was growing and spreading because he is NTRK-3 positive.
In what line of therapy were you prescribed/given Larotrectinib (VITRAKVI) for the treatment of your cancer?	First Line	Third Line	First Line	second line
Did you participate in a clinical trial in connection to this drug? If yes, please specify clinical trial name and location:	APEC14B1, The Project: Every Child Protocol: A Registry, Eligibility Screening, Biology and Outcome Study. USA, Minnesota	Larotrectinib trial in Seattle Washington USA	Yes, New York	No
How long have you been taking Larotrectinib (VITRAKVI)? Please specify below:	6 months	40 months	21 months	Five months.
If applicable, did you change your treatment option to Larotrectinib (VITRAKVI) after recurrence*? If yes, why?*If cancer is found after treatment, and after a period	No	Yes, Radiation was no longer working.	N/A	N/A

	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
of time when the cancer couldn't be detected				
In your opinion, is there a particular gap or unmet patient need with current therapies that Larotrectinib (VITRAKVI) will help alleviate?	Yes, Chemo and radiation would not have worked on our son's tumor. If he would have had surgery right away, he would have had morbid surgery with the possibility of losing his leg.	Yes, Works very well with little side effects	Yes, Further testing is needed to identify patients with NTRK fusions	Yes, THIS is what Vitrakvi is all about. How many stage IV cancer patients are you aware of that work full time, play hockey, mow the lawn, walk the dog, help with homework and everything else expected in a young family. Vitrakvi allows patients to feel human again. And if the cancer does come back, isn't it amazing that the patient was able to have 'normal' time with family before the pain and sickness returns? If ever?
What effect do you expect (or hope) that Larotrectinib (VITRAKVI) will have on the cancer and your prognosis?	Reduce the size of tumor so it can be removed from his leg without having morbid surgery	Maintain or improve quality of life, Increase overall survival, Reduce side effects from current medications or treatments, Ease of use	Maintain or improve quality of life, Increase overall survival, Ease of use, Enable my son to have non-mutilating surgery to remove tumor	Maintain or improve quality of life, Increase overall survival, Delay onset of symptoms, Delay need for chemotherapy, Ease of use
Which symptoms does Larotrectinib (VITRAKVI) manage better than the existing therapies?		Has few side effects and works		All of them.
Which symptoms does Larotrectinib (VITRAKVI) manage less effectively than the existing therapies? Please describe below.		None		None.
Was Larotrectinib (VITRAKVI) able to shrink/control your cancer and/or spread of the	Yes	Yes	Yes	Yes

	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
disease to other organs (metastases)?				
What side effects have you experienced while on Larotrectinib (VITRAKVI)?	Tiredness, constipation, weight gain, frequent headaches	joint pain/muscle pain	Neutropenia which was resolved with a 25% dose reduction	Tiredness, joint pain/muscle pain, weight gain, numbness and tingling in hands
Of the side effects experienced with Larotrectinib (VITRAKVI), which ones were most difficult to tolerate? Please identify your top three.	headaches, tiredness, weight gain	Joint pain if medication is taken late.		Numbness and tingling in hands but it wasn't particularly difficult. None of the side effects of Vitrakvi are worse than chemotherapy and radiation. In fact, they don't even come close and we would consider them minor in comparison.
On a scale of 1-10, with 1 being "no side effects at all" and 10 being "debilitating side effects that impact daily living", how would you rate your side effects while taking Larotrectinib (VITRAKVI)?	3	no side effects at all1	no side effects at all1	2
Did you have to stop the Larotrectinib (VITRAKVI) earlier than planned or did you have to skip doses due to side effects?	No	No	No	No
As an oral therapy (drug administered through your mouth), has Larotrectinib (VITRAKVI) been easy to administer/receive?	Yes	Yes	Yes	Yes
On a scale of 1-10, with 1 being "low/severely impacted", and 10 being "high/normal living", how do you rate your quality of life	9	high/normal living10	high/normal living10	high/normal living10

	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
while taking Larotrectinib (VITRAKVI)?				
Were you able to continue your daily activities or work while undergoing/after completing Larotrectinib (VITRAKVI)?	Yes	Yes	Yes	Yes
Do you find Larotrectinib (VITRAKVI) to be easy to integrate in your daily routine?	Yes	Yes	Yes	Yes
What is/are the most difficult aspect(s) of Larotrectinib (VITRAKVI) for you?	Monetary concerns (absence at work, driving expenses, etc.), fatigue	Hours spent in medical appointments, Monetary concerns (absence at work, driving expenses, etc.), anxiety/worrying	No particular issues	The worry that it won't be covered by our private insurance or our government insurance. If the tumours are inoperable and the other therapies won't work, the worry that Vitrakvi will not be available in Canada is very difficult.
Do you believe Larotrectinib (VITRAKVI) will change your long-term health and well-being for the better?	Yes, The cancer is gone!	Yes, Stopped / reduced the disease load	Yes, The treatment has been very easy to tolerate and shrank my son's tumor by over 98% allowing for curative surgery in the near future.	Yes, It has already given back so much. An actual normal life. 'Living' with stage IV cancer.
Based on any experience you have had taking other drugs for your cancer: On a scale of 1-10, with 1 being "much worse" and 10 being "much better", how would you rate your overall experience with Larotrectinib (VITRAKVI)		much better10	N/A	much better10

	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
compared to other treatments?				
Did accessing Larotrectinib (VITRAKVI) 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.	Yes, he would have lost his leg in surgery if there would not have been this medication.	Got off of oxygen. Didn't die. Available to Live a normal active lifestyle		Yes. It's allowed him to live a productive and 'normal' life. He would not be living the same way on chemotherapy or with radiation treatments. And again...playing hockey twice per week. :)
Is Larotrectinib (VITRAKVI) approved where you reside?	Yes	Yes	Yes	Yes
How was Larotrectinib (VITRAKVI) funded for you?	Clinical Trial	Clinical Trial	First on clinical trial and then funded by insurance	Insurance Plan, Special Access Program
Do you believe Larotrectinib (VITRAKVI) should be funded where you reside for the treatment of cancer? Why or why not.	Yes, This is the only treatment that would work on our sons cancer.	Yes, Works well. Little change to quality of life. Might be available to skip other treatment (chemo, radiation, surgery)	Yes, This is the future of cancer treatment; a medication with relatively no side affects, significant tumor response and the possibility for a non-mutilating curative surgery	Yes, My husband has had every treatment 'normal' for cancer: surgery, chemo, and radiation and Vitrakvi is the only treatment that allows him to live a normal life with little to no side effects and success with significant tumour shrinkage. It's been our 'miracle' drug.
Did you experience any financial constraints due to Larotrectinib (VITRAKVI)?	No	Yes	No	No
Have you had issues accessing Larotrectinib (VITRAKVI)? If so, what issues have you experienced?	I haven't had any issues accessing therapy	Not available in my cancer center/hospital, Did not have access to a clinical trial, No provincial coverage, Travel costs associated	I haven't had any issues accessing therapy	I haven't had any issues accessing therapy

	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
		with accessing therapy/treatment		

7. Companion Diagnostic Test

Nine out of thirteen (69%) patients confirmed they tested positive for the unique biomarker, the NTRK gene fusion. None of the patients expressed concern or difficulty having accessed the testing centre. As reported in Tables 9-11, patients and caregivers expressed the significance of biomarker testing to them, as their gene matched the drug under review which saved or prolonged their lives. When asked about a particular gap or unmet patient need, patients and caregivers highlighted the importance of molecular profiling: *"all new patients should have NGS testing on their solid tumor mass"* (Patient 4), *"further testing is needed to identify patients with NTRK fusions"* (Caregiver 4). Most patients had their biomarker testing done after diagnosis, which emphasizes the need to adopt biomarker testing as a standard practice at diagnosis in Canada. Specifically to colorectal cancer, while it's true that NTRK-gene fusions are rare in sporadic colorectal cancers (1-2%), this mutation may also be present in colorectal cancers that display MSI (15-20%). As NTRK fusions are found in patients with MSI-H colorectal cancer, Larotrectinib may be the next line treatment clinicians can rapidly transition to if patients are not responding to the initial therapy as expected.

The qualitative data on the companion diagnostic test is summarized and represented in Table 12 (surveyed patients), and Table 13 (Surveyed caregivers). For this section, Caregiver 1 did not respond to any of the questions and is therefore not shown in the table. Telephone interviewed patients were not asked these specific questions.

Table 12: Surveyed Patients – Companion Diagnostic Test

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
What methods were used to diagnose your cancer?	CT scan, biopsy	Incidental Finding / Physical Exam at Family Doctor, CT scan, Reporting of symptoms and/or discomfort, blood work	Incidental Finding / Physical Exam at Family Doctor, CT scan, biopsy, blood work	CT scan, biopsy, Reporting of symptoms and/or discomfort	CT scan, biopsy, Reporting of symptoms and/or discomfort, ultrasound	CT scan, biopsy, Reporting of symptoms and/or discomfort, blood work
Did you have one or more biopsies to further investigate the make-up of your tumour(s)?	Yes	No	Yes	Yes	Yes	Yes
Prior to your diagnosis, were you aware that biomarkers can help to determine a specific treatment option for you?	No	No	Yes	Yes	No	No
Did your oncologist or any other member of your medical team explain biomarker testing (or tumor profiling) before treatment started?	Yes	No	Yes	Yes	Yes	No
Do you recall having biomarker testing before or after being diagnosed with cancer?	After diagnosis	After diagnosis	After diagnosis	After diagnosis	After diagnosis	Before diagnosis
If you have you been tested for any other biomarkers, which biomarker did you test positive for?	NTRK	I don't know	NTRK	.	NTRK	.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
If you had your biomarkers tested, what treatment did your oncologist first select?	Chemotherapy, radiation therapy	radiation therapy	Targeted therapy (Larotrectinib)	Chemotherapy	Chemotherapy, Capcitobine Temozolamide	

Table 13: Surveyed Caregivers – Experience with Drug under Review

	Caregiver 2	Caregiver 3	Caregiver 4	Caregiver 5
What methods were used to diagnose your cancer?	Incidental Finding / Physical Exam at Family Doctor, CT scan, biopsy, MRI	Incidental Finding / Physical Exam at Family Doctor, CT scan, biopsy, blood work	biopsy, FISH testing to identify ntrk fusion	CT scan, biopsy, Reporting of symptoms and/or discomfort
Did you have one or more biopsies to further investigate the make-up of your tumour(s)?	No	Yes	Yes	Yes
Prior to your diagnosis, were you aware that biomarkers can help to determine a specific treatment option for you?	No	No	Yes	No
Did your oncologist or any other member of your medical team explain biomarker testing (or tumor profiling) before treatment started?	Yes	I don't recall	Yes	I don't recall
Do you recall having biomarker testing before or after being diagnosed with cancer?	Before diagnosis	After diagnosis	Before diagnosis	After diagnosis
If you have you been tested for any other biomarkers, which biomarker did you test positive for?	NTRK	NTRK	NTRK	NTRK, HER2
If you had your biomarkers tested, what treatment did your oncologist first select?	Targeted Therapy (latrotrectinib)	.	Targeted therapy (Larotrectinib)	Targeted therapy (Larotrectinib)

8. Biosimilar

N/A

9. Anything Else?

The thirteen patients/caregivers provide ample confirmation that the drug under review prolongs overall survival, improves quality of life, and majorly reduces their cancer symptoms with tolerable side effects from the drug. At the same time, they provide evidence that molecular profiling can personalize therapy for patients to optimize outcomes. The drug under review, Larotrectinib, serves as an example of precision oncology practice that can improve the lives of cancer patients. Patients and caregivers provided heartfelt and compelling comments on why Larotrectinib should be accessible to anyone with NTRK fusion. Patient 7 says that today he is *"a productive member of society and [has] been spared a horrible fate"*. He goes on to say that "*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"*. Patient 8 made sure to note that *"even though this drug impacts a small group of people, it has an enormous ripple effect and has an impact socially, economically, emotionally, and psychologically on the family, the work environment, and the patient themselves"*. Caregiver 5 stressed that Larotrectinib *"allows patients to feel human again. And if the cancer does come back, isn't it amazing that the patient was able to have 'normal' time with family before the pain and sickness returns? If ever?"*

Patient 7 has done a patient testimonial video in 2019 with the American Association for Cancer Research [redacted]
In the video, he explains how he could feel the tumours all over his body shrink after only 4 days of taking Larotrectinib, and after the end of 4 weeks all his tumours were gone, except one which shrunk by 65%.
"It did not make me sick, it was amazing".

Based on the objective research carried out as represented herein, Colorectal Cancer Canada strongly urges that a positive funding recommendation be issued for Larotrectinib for the treatment of patients with NTRK gene fusion positive tumours. We believe it is essential to provide these patients equitable access of effective drugs that improves their quality of life and outcomes as well as the impact on their families, unaccompanied by any financial restrictions. Providing molecularly targeted therapies that are easily administered with minimal side effects, and permit patients to carry on normal lives is fundamental for basic and high quality care in Canada.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie Corp			x	
Amgen Canada				x
AstraZeneca Canada				x
Bayer Inc				x
Boehringer Ingelheim Ltd			x	
Bristol Myers Squibb Canada				x

Celgene Corporation			x	
Eli Lilly Canada			x	
GlaxoSmithKline				x
Hoffman-La Roche				x
Janssen Inc			x	
Merck Canada Inc.			x	
Novartis Pharma Canada			x	
Pfizer Canada				x
Taiho Pharma Canada				x

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Barry D. Stein
Position: President
Patient Group: Colorectal Cancer Canada
Date: December 4, 2020

CADTH

CADTH Drug Reimbursement Review
Patient Input Template

Name of the Drug and Indication	Larotrectinib (Vitrakvi) 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.
Name of the Patient Group	Lung Cancer Canada
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

Lung Cancer Canada is a registered national charity and is the only organization in Canada focused exclusively on lung cancer.

Lung Cancer Canada is registered with CADTH.

2. Information Gathering

- Data collection: The information was collected through interviews and environmental scans. The thoughts and experiences of the patients have been included in the submission. The information was accessed November – December 2020.
- Demographic data:
    - The requested treatment is currently not available in Canada. Input collected from patients on currently available treatments is discussed in the treatment sections.
    - LCC also utilized information from previous larotrectinib submissions.
    - The NTRK is found to be more common on non-smokers or light smokers
    - The population of NTRK positive NSCLC patients is extremely small, lung cancer cases just 0.2%.

Gender	Age	Patient/Caregiver	Source	Location	Input
Male (JP)	61	Patient	Interview	Canada	New
Male (QB)	66	Patient	Interview	Canada	New
Female (AN)	33	Patient	Environ Scan	Online	New
Male (EF)	64	Patient	Environ Scan	Online	Previous Submission
Female (NM)	N/A	Patient	Environ Scan	Online	Previous Submission
Male (DL)	N/A	Patient	Environ Scan	Online	Previous Submission

3. Disease Experience

In the fall of 2013, JP, a non-smoker received devastating news, he not only had lung cancer, but also had stage 4 non-small cell lung cancer (NSCLC) that had spread to his brain, bones and liver. This was an unexpected diagnosis and a huge shock for his family, and he was overwhelmed with sadness and worried about his family losing a husband and father.

He was initially treated with chemotherapy and subsequently immunotherapy, but he eventually progressed. Following discussions with his oncologist, JP's tumour samples were sent for testing and he was found to have the genetic mutation NTRK, and there was a possibility that a targeted treatment, larotrectinib would work for him. This treatment is approved by the FDA and is currently available in the United States and the United Kingdom, but is not available in Canada.

In April, 2019, JP started larotrectinib, and in his words, "right off the bat, it showed great results."

Lung cancer is the most commonly diagnosed and leading killer of all cancers in Canada, accounting for 25% of all cancer deaths, and the 5-year survival rate is just 19% (Canadian Cancer Statistics, 2020), with lower rates for advanced cases. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, occurring in 80-85% of cases, with several known mutations. Some of these mutations include ROS1, EGFR, ALK and NTRK.

The neurotrophic receptor tyrosine kinase (NTRK) gene fusion which has been found in multiple tumour types, has a prevalence of about 1 – 2 % and occurs in about 0.2% of lung cancer patients, most of whom are non-smokers or light smokers. This type of lung cancer is extremely rare.

In recent years, targeted therapies have emerged as an important treatment option for patients with targetable mutations such as ROS1, EGFR and ALK. These treatment options have been shown to have lower toxicities compared to the current standard of care, and help control the disease while allowing patients have a good quality of life with manageable side effects. The treatments have given patients and their families hope, hope to live longer, hope to spend time with their loved ones, hope to stay functional and active, and be able to continue working and enjoy living. The NTRK mutation currently does not have any available treatments in Canada. This is unfair, why should patients be denied access to viable treatment options that have been shown to work and give patients the chance to live longer and better. These are treatments that can help address this unmet need.

A diagnosis of advanced lung cancer can leave patients like as JP overwhelmed, causing them to worry about survival and their loved ones. Viable treatments options that can help treat their cancer should not be one of their worries.

Larotrectinib, an NTRK inhibitor, which has been approved by the FDA for the treatment of patients with solid tumours that have a neurotrophic receptor tyrosine kinase gene fusion, is a treatment option that should be considered for this group of patients. This treatment option is what was given to EF, who was diagnosed with stage 4 NTRK positive cancer 3 years ago. He was still able to work as a high school basketball coach and even had a championship season and achieved his 400th win.

4. Experiences With Currently Available Treatments

Currently, NSCLC patients with no targetable mutations are treated with chemotherapy, immunotherapy or a combination of both treatments. However, based on recent research studies it is well recognized that patients with targetable mutations do better with targeted treatments compared to the above-mentioned treatment options.

Chemotherapy

Works to treat the cancer

This systemic form of treatment, given via the intravenous route is a viable form of treatment and continues to play an important role in the management of lung cancer. This form of treatment helps to shrink tumours and improves patient's symptoms, but patients eventually progress on this form of treatment.

Over the course of about 4 years, JP was treated with 3 different types of chemotherapy. One treatment helped control the cancer for about 2 years and the others between 3 to 10 months. He progressed on all of these treatments.

In some cases, this form of treatment does not work. Take QB for example, he was treated with chemotherapy twice, but there was never any shrinkage in the size of his tumour. He kept progressing quickly with the treatments.

Even AN, after 6 months into her treatment, chemotherapy did not work. She was eventually switched to another chemotherapy, which still didn't work.

Affects patient's functionality and interfered with life activities

Some patients treated with chemotherapy experience side effects that interfered with daily activities. 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. Some patients needed significant recovery time after each infusion, and this took away time that could have been spent at work or with their loved ones.

For JP, chemotherapy was a challenge. He felt sick most of the time and was unable to do much or be involved in many activities.

Side effects

While some patient's on chemotherapy experience minimal symptoms, some reported side effects consistent with other reports of those on chemotherapy such as extreme fatigue.

JB experienced extreme fatigue with chemotherapy, felt very sick most of the time, could not do much physically, and required a lengthy time to recuperate before his next treatment. He also developed permanent hearing loss with chemotherapy and subsequently had to be fitted with a hearing aid.

QB also experienced bad side effects with chemotherapy. He developed swelling in his legs and feet, extreme fatigue, blood clots and constipation. In his words, “I had no zeal to live.”

Chemotherapy can also affect patient’s ability to work and this can result in financial hardship for the families.

Immunotherapy

Immunotherapy is a form of treatment that has allowed many patients to hope for improved outcomes and has been shown to improve quality of life with more manageable side effects.

The NTRK positive patients that provided input and were treated with immunotherapy say this treatment was much easier that chemotherapy, however, for both JP and QB, the treatment did not work. JP was treated with immunotherapy for 6 months, and although he had no side effects with the treatment, it did not work, and he subsequently progressed. For JP, immunotherapy was a much better experience than chemotherapy, however, it did nothing for his cancer.

Impact on Caregivers

No caregivers caring for their loved ones with experience on larotrectinib provided input for this section. The input provided is from input from previous surveys, interviews and environmental scans.

A diagnosis of lung cancer affects not only the patients but their loved ones too. With a survival rate of 19% many caregivers worry about the survival of their loved ones.

Many caregivers are involved in the care, well-being and management of their loved ones, including helping them cope with the symptoms of the disease and the side effects of treatment. With certain treatments such as chemotherapy and immunotherapy, which are given via the intravenous routes, there is an added burden to take their loved ones for their treatments and care for them afterward, as it is well documented some of these treatments have toxic side effects. In some cases, caregivers may need to take time off work to provide this care, which could lead to a reduction in productivity and sometimes financial and even mental stress, which in turn could affect their ability to care for their loved one.

With oral medications such as larotrectinib, this form of delivery would lessen a significant amount of stress and dependency on caregivers, as patients would be able to go for their appointments themselves and caregivers would be more productive at work.

JP’s spouse had to take a couple of months off work when he was treated with chemotherapy to take him for his hospital visits and help him recuperate after treatments. With larotrectinib, she has not had to take time off work.

5. Improved Outcomes

Improved outcomes for patients would include:

- Control the cancer

- Improve symptoms
- Manageable side effects
- Effective on the CNS
- Delay progression
- Extend survival with a good quality of life
- Provide longer lasting and durable treatment

All of these align with patients' values.

6. Experience With Drug Under Review

The requested treatment is currently unavailable in Canada. Lung Cancer Canada was only able to source input from a limited number of patients. Their thoughts and experience with larotrectinib are discussed below. The population of NTRK positive NSCLC patients is very rare, extremely small in numbers, occurring in about 0.2% of lung cancer patients. Additionally, this submission is asking for funding in cases where there are no other viable treatments. Unfortunately, this means that the potential population that can benefit from the treatment is further decreased.

Larotrectinib worked to treat the cancer and improved symptoms

Treatment shrunk patients' tumours:

When JP was told about larotrectinib, he was excited, hoping for a breakthrough that would treat his cancer. He was also anxious and worried whether the treatment would work for him. Turns out it did work, which made him really glad. He started larotrectinib 18 months ago. His first scans after starting larotrectinib showed great results with no new cancer, there was some shrinkage and some tumours had disappeared. His cancer was stable and he says this treatment saved his life.

JP did stop taking this treatment for 2 days due to the development of a clot in the lung (this was unrelated to the treatment). Recent scans 2 months ago showed his brain remained clear and the spot in his liver was gone.

QB was diagnosed in 2017, with spread to his liver and bones. Having previously received chemotherapy and radiation, then immunotherapy and then more chemotherapy with no success, for him larotrectinib was his last hope. He started larotrectinib, December 2019 and has seen an improvement over his previous treatments. A previous scan showed no liver metastasis, and a recent one showed one spot in the liver. Apart from that, he has no other evidence of disease. This he says has given him renewed hope

For AN, after a number of failed treatments, a sample of her tumour was sent for testing, she was found to have the NTRK fusion mutation, and was placed on larotrectinib in 2016. While she had a small recurrence after months of treatment, that was radiated, she currently shows no evidence of disease.

Improved patients symptoms:

JP started feeling better as soon as he started taking the drug. For him, this was the first time his cancer had ever been stable and he felt so much better physically and mentally. He calls it a miracle drug. The treatment also helped to resolve some of his back and hip pain.

Due to previous chemotherapy, JP has some residual side effects and mobility issues. However, since starting treatment his hips also don't hurt as much anymore. It should be noted, JP had radiation to the hip to treat the cancer and subsequently developed arthritis. This has been treated with steroids.

QB had been placed on pain medication due to the cancer, but since staring larotrectinib, his doctors are looking to reduce his medication at his next visit.

NM's tumour occupied 90 percent of her lungs, was on oxygen and in a wheelchair. After genomic testing and looking for viable treatment options, she was placed on larotrectinib. Four weeks after beginning treatment, she was able to take her kids to the movies, and even celebrate her birthday.

Within 72 hours of treatment, DL no longer needed a cane, and within two weeks, he was walking around the city, playing with his kids and eating like a champ.

Larotrectinib allows patients to be functional and be involved in life's activities

Functionality:

JP's appetite improved since starting larotrectinib. He had lost quite a bit of weight and was unable to eat much due to the metallic taste in his mouth caused by previous treatments. His appetite returned to normal since starting larotrectinib, and he has even gained weight. He feels much better mentally and physically.

He has been able to move around a lot more, and apart from the residual side effects from previous treatments, he would say he has a very good quality of life. This was a huge change for JP who on previous treatments was unable to do much around the house.

Since her treatment with larotrectinib, AN has been able to return to work. She went from failed chemotherapies that affected her quality of life, to starting larotrectinib, which has allowed her to go back to work.

Involvement in life's activities:

Because of larotrectinib, JP was able to celebrate his 60th birthday, he saw the birth of his grandson and also got to attend his daughter's graduation from teacher's college. He is has been able to be a part of many joyful moments with his family.

He was however, unable to go back to work as a result of the side effects from his previous treatments based on how he feels on larotrectinib, and he believes he would have been able to return to work. He has been able to participate in more family activities, though he has been unable to see and hang out with friends due to the pandemic

AN is now buying a home with her husband. This treatment has allowed her to get better and now she has the option to buy a house with her husband. This is something she was not able to do or consider on her previous treatments.

EF was still able to work as a high school basketball coach and even had a championship season and achieved his 400th win.

Dosage route

All patients interviewed were especially happy to have a treatment that is given via the oral route. Many patients are fearful of intravenous treatments, which causes them worry and develop mental stress even before the treatment is given.

Larotrectinib is given as a pill or liquid dose. For many patients, the availability of these different options provides flexibility especially for patients that may have conditions or co-morbidities that may not allow them receive the treatment via a particular route. Some patients may be unable to swallow, for e.g. patients with head or neck cancers, some may be weak, fatigued or have a poor appetite, all of which can affect the dosage choice. Having more dosage options is a significant advantage of this treatment.

According to JP, the pills and liquid have been easier and have saved him a lot of trips to the hospital, saving him money, time and reducing stress on him and his family. In his words, "what could be easier than this treatment?" QB says, the oral therapy is easy to take, especially since it is a liquid."

Patients value a treatment that not only improves symptom control, has better disease control, allows for a better quality of life, but is also easy to administer.

Side effects were manageable

The most common side effects with larotrectinib are myalgia, cough, dizziness, diarrhea, fatigue, constipation and dizziness.

JB has had just mild fatigue since staring this treatment. According to him, this treatment would spare patients some of the side effects he experienced with chemotherapy and radiation, which still linger such as short-term memory loss, dizziness and hearing loss. He had to give up driving due to the effect on his cognitive skills. He believes this could have been avoided if he had been placed on larotrectinib earlier.

QB has only experienced slight tiredness since starting treatment with larotrectinib. For AN, larotrectinib she says, did not make her sick unlike her previous treatments.

For many of these patients, larotrectinib was their last hope. They had previously been treated with chemotherapy and immunotherapy but they either progressed or the treatment just didn't work. Larotrectinib rescued these patients by not just working but working well, it also helped extend patient survival. This is consistent with the input from the previous larotrectinib submission. The above input showed that larotrectinib helped improve patients' symptoms and the disease was well controlled.

7. Companion Diagnostic Test

In the previous submission, CADTH was concerned about that testing for the NTRK biomarker would lead to a high cost burden on the health system. However currently that concern is mitigated by several factors. Larotrectinib is used where there are no other satisfactory treatment options. In many cases, this is after other medications have failed. Due to this, unfortunately this means that not all NTRK patients are going to be alive to take advantage of larotrectinib. This decreases an already small population. IHC is a very cost effective testing methodology and is used to screen for the NTRK biomarker. Only cases that screen positive are sent for NGS. Further reducing is a manufacturer program, FastTRK, that commits to covering the cost of all patients who need testing to detect the NTRK fusion. Additionally, since the last submission, provinces like Nova Scotia, who already used NGS, are moving to expand their panel to cover NTRK and other biomarkers. Others are examining how to use NGS as a standard of care. This means that testing for NTRK will not add pose an additional cost burden on the system.

8. Anything Else?

With the progress in cancer treatments in recent years, particularly with the identification of actionable mutations and targeted therapies, as evident with the ALK and EGFR inhibitors, these targeted treatments are redefining patient survival. They have been shown to be efficacious in treating the cancer, providing durable responses and manageable side effects, while allowing patients to continue being active, functional and independent. It is also well recognized and discussed within the medical community, patients with a targetable mutation respond to targeted treatment better than the standard forms of treatment, resulting in better outcomes for patients.

With many of these advanced cases also having CNS involvement at diagnosis or along the course of their journey, it is also important to provide patients with an option that can treat any brain metastasis. Take JP who had to go through whole brain radiation which left him with long lasting cognitive side effects including short term memory loss and dizziness that affected his quality of life. The phase 2 data results that were presented at the European Society of Medical Oncology (ESMO) Virtual Congress 2020 showed that larotrectinib had not just a high response rate and long duration of response, but was also significantly active on the CNS. It should also be noted, patients with the NTRK fusion mutation make up

a small population, and it is an extremely rare type of cancer, thus it is unlikely a phase 3 study will be carried out.

In the previous submission, pERC gave a negative recommendation because it was uncertain that there was a net clinical benefit of larotrectinib treatment compared with available treatment options. LCC believes the patient input provided and the updated data from the clinical trial show that larotrectinib does provide a clear clinical benefit not just for lung cancer but also the different tumour groups. This follow up data should provide more certainty with regards to the efficacy of larotrectinib, and LCC believes this addresses any uncertainties concerning its clinical benefit and as such larotrectinib would meet the criteria and expectations of CADTH.

pERC also had concerns about the high cost burdens. LCC believes negotiations between the PCPA and manufacturers can help facilitate a more cost effective pricing. Concerns in regards to the cost of the testing have been alleviated with the increased/expanded use of NGS as a standard of care and the manufacturer's commitment to support for testing.

This disease has a poor prognosis and comes with a significant burden, and as seen with the input received from patients, many had no previous satisfactory form of treatment or progressed on the treatments they were given. For these patients. larotrectinib was their last hope. The input shows patients on this treatment had improved symptoms, were able to be independent, functional and physically active, and this is significant and meaningful. We hope the CADTH provides a positive recommendation for larotrectinib, not just for lung cancer but across all tumour groups.

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3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer			X	

4.

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Christina Sit
Position: Programs Manager
Patient Group: Lung Cancer Canada
Date: December 4, 2020

CADTH

CADTH Reimbursement Review
Patient Input Template

Name of the Drug and Indication	**Larotrectinib/Vitrakvi** Indication: 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.
Name of the Patient Group	**Sarcoma Cancer Foundation of Canada**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

The SCFC is Canada's national sarcoma cancer charity. We support patients and their families, while working with Canada's leading researchers in their efforts to eradicate sarcoma cancers.

It is our mission to connect patients and their families with the best medical information and community resources, to ease the process of dealing with a sarcoma cancer diagnosis and treatment. Our work focuses in three main areas: patient support, including education and advocacy, disease awareness, and support for Canadian sarcoma cancer research.

For more information, please visit our website at www.sarcomacancer.ca.

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

We are based in Canada and collected data here from both male and female patients who received their treatment in both the US and Canada (age range 30-50). We conducted multiple, indepth interviews with 3 patients with direct experience with the drug under review as well as 2 caregivers and several physicians across Canada. In addition to that, our answers containing more general sarcoma cancer information are arrived at by sharing personal experience, as well as the collective experience of our membership and community over the more than 10 years since our organization was founded.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Sarcoma is an invasive and aggressive cancer. As there are many subtypes (over 70 soft tissue sarcomas alone), there are many different patient experiences, but 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 radiation, chemotherapy 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. 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 about which they are passionate due to their disease. In the event that surgery is not an option and a patient embarks on 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. Caregivers are then 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. We have 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.

In terms of managing disease, the immediate need is to relieve the physical symptoms to allow for some quality of life. Severe pain is a very typical symptom, as are those listed above, and many patients are confined to bed or a wheelchair if they are unable to find

effective treatment. Because sarcoma cancer is a rarer cancer, the community is generally underserved in terms of research funding and also development and access to new, promising treatments. Any new option that gives physicians an additional tool in treating this complex and difficult cancer is of great help to patients and their support systems.

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Sarcoma affects patients in a variety of ways given its many subtypes. 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. We spoke to patients who described radical transformations from larotrectinib, resulting in quick and effective resuming of all daily activities. Patients are able to return to work and be present with their families and get back to living their lives. We have heard from patients and caregivers that larotrectinib was the difference between dying in their 20s and living to become the father of twins and enjoy a full life. It is the difference between dying in your early 40s or living to see your children through high school. In all patients we interviewed, the results were incredibly effective and quite immediate. In all of our hundreds of patient interactions over the past decade and in the personal experience of those involved in our organization, we have seen that this type of result is extremely uncommon among existing non-surgical treatments. Patients 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 patients are now a number of years out from their initial treatment with no discernable side effects. While we have seen some treatments in recent years come to market that have increased life expectancy or halted disease progression somewhat, this transformational treatment represents a new level of hope and potential for Canadian patients. Given the lack of effective soft tissue sarcoma treatments, larotrectinib is a critical tool for Canadian patients and physicians.

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

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, ease of breath, etc. as a significant improvement. Sarcoma cancer patients often experience quick disease progression that, without intervention, will halt their lifestyle and activitiy and eventually result in death. What we have heard in our interviews about larotrectinib is that it essentially "melts away the tumours" so that patients are effectively disease free. The patients with whom we spoke were several years beyond their treatment and had not experienced any disease regression or reappearance of tumours. One patient 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. He 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 patients we spoke to reported no side effects of treatment and were amazed at the speed with which the treatment began to work. For the patients in whom this treatment is effective, it has been a life-saving and life-changing solution. Caregivers describe a radical transformation 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 patients we interviewed.

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

We spoke to patients who accessed their drug under review via clinical trial and via private insurance. They all described an incredible process of being in the last stage of life to being disease free. Given that there were no side effects for any of the patients, there was no disadvantage to the treatment. For patients that exhibit the NTRK fusion gene, this treatment would be an incredible option – one we dearly hope that all Canadian patients will have the opportunity to access and not only those with the funds or insurance to do so.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

Patients spoke of the ease of receiving the genomic testing and are all purponents of these tests being widely available. Given the effectiveness of this treatment, it would be wonderful if patients could be tested to determine if they are appropriate candidates.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

The results that patients have experienced with larotrectinib are uncommon and exciting. In a patient community who too often have nowhere to turn for effective treatment options, larotrectinib represents a great step forward and much needed hope.

CADTH

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Bayer Canada				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Diana Arajs
Position: Chair
Patient Group: Sarcoma Cancer Foundation of Canada
Date: December 4, 2020