CADTH

CADTH Reimbursement Review

Patient Input

tucatinib (Tukysa)

Seagen Canada Inc.

Indication: Advanced or Metastatic Breast Cancer

CADTH received patient input from:
Canadian Breast Cancer Network
CanCertainty
Rethink Breast Cancer

April 23, 2021

CADTH

CADTH Reimbursement Review
Patient Input

Name of the Drug and Indication	In combination with trastuzumab and capecitabine for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine, separately or in combination.
Name of the Patient Group	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

As a member of the Canadian Cancer Action Network, the Canadian Breast Cancer Network is committed to adhering to the Code of Conduct Governing Corporate Funding.

2. Information Gathering

Information for this submission was collected via:

CBCN's 2017 Metastatic Breast Cancer Patient Survey: An online survey conducted by the Canadian Breast Cancer Network, distributed to patients living with metastatic breast cancer. 180 metastatic patients participated in the survey, with 36 individuals identifying as being HER2+. 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.

CBCN's 2012 Metastatic Breast Cancer Patient and Caregiver Survey Report: An online survey, conducted in collaboration with ReThink Breast Cancer, 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

Key informant interviews: Phone interviews were conducted in November 2020 and February 2021 with 2 Canadian metastatic breast cancer patients living with HER2+ metastatic breast cancer that had direct experience with the treatment under review.

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 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, and is often more severe. It is most commonly spread to the bones, but can include the lungs, liver, brain and skin. 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. 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 possible 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 Patient 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;
- 39% of patients reported that insomnia resulted in a significant or debilitating impact, and 46% 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 Metastatic Breast Cancer Patient Survey (2017 Survey).

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 be social and meaningfully participate in their community. When asked in

the 2012 Survey what kind of impact living with metastatic breast cancer has had on their quality of life:

- Among those who were employed, 71% of patients identified significant restrictions to their ability to work;
- Among those with children or dependents, 21% identified significant restrictions and 53% reported some or moderate restrictions to their caregiving responsibilities;
- 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 included: guilt, the feeling of being a burden on caregivers, fear of death, poor body image, not knowing what functionality will be lost, fear of the impact of cancer and the loss of a parent on children, not knowing what will happen to children, the loss of support of loved ones, as well as marital stress/loss of fidelity and affection from husband.

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.

In our 2017 Survey, the majority of respondents experienced metastases to their bones, liver and lungs.12% of metastatic patients reported metastases to their brain while 20% reported metastases to other body parts. Most of the HER2+ metastatic breast cancer patients (30 patients) had been or were currently being treated with chemotherapy, 25 patients had surgery, 19 patients had or were receiving hormone therapy and 13 patients had or were receiving radiation therapy.

The first line of treatment for patients with HER2+ metastatic breast cancer is trastuzumab plus pertuzumab and a taxane, followed by second-line trastuzumab emtansine. If there is disease progression after this, there is no specific standard of care therapy.

Specifically in the case of brain metastases, while systemic therapies have improved, incidence rates of brain metastases in breast cancer patients have increased, developing in about half of patients. Effective treatment options for HER2+ breast cancer in patients with brain metastases are limited; treatment options include local

therapies such as neurosurgical resection and stereotactic radiation therapy. Trial data showing the effectiveness of some of these systemic therapies is lacking.

Key Factors for Decision-Making Around Treatment
Respondents in our 2017 Survey indicated that the following key factors influenced their decision-making around treatments:

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 HER2+ metastatic patients in our 2017 Survey revealed that efficacy of the treatment is critical to their decision-making. 72% of them indicated that progression-free survival of less than 3 months was important or very important, 80% indicated that progression-free survival of 3-5 months was important or very important and 86% indicated that progression-free survival of 6 months or longer was important or very important. When asked about overall survival, 80% of the HER2+ metastatic patients indicated that overall survival was important or very important when considering treatment options.

Metastatic patients in our 2017 Study also spoke on the importance of effectiveness in their decision-making anecdotally:

> *"The most important factors for me are progression free survival and quality of life."*
> *"Anything to prolong my survival and maintain quality of life."*
> *"Survival is of upmost importance to me."*

Quality of life:
Quality of life was routinely cited by patients as a key factor in making treatment decisions. In our 2017 Survey, 72% of the HER2+ metastatic breast cancer patients revealed that quality of life was important or very important to them when considering treatment options.

This concern was reiterated anecdotally:

> "*Effectiveness but also quality of life."*
> *"Survival rate chances is paramount, followed by quality of life."*
> *"Quality of life over quantity."*
> *"Definitely the balance of quality of life vs side effects with the [effectiveness]."*

Patient willingness to tolerate treatment side effects:
In our 2012 Metastatic Patient and Caregiver Survey, the responses to 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 was shown to be determined at the personal level.

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.
- 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.

Similar responses were also found in our 2017 Survey. The majority of HER2+ metastatic breast cancer respondents indicated that **pain, fatigue, nausea, lack of concentration, diarrhea, insomnia, and hair loss** were very acceptable or somewhat acceptable symptoms in exchange for 6 months or less of benefits from breast cancer treatment. The majority of HER2+ metastatic respondents indicated that **depression** as a symptom in exchange of 6 months or less of benefits from breast cancer treatment was somewhat acceptable (15 respondents) or not acceptable (9 respondents). Similarly, the majority indicated the **memory loss** would be somewhat acceptable (15 respondents) or not acceptable (8 respondents). When it came to the symptom of **vomiting**, 14 HER2+ metastatic respondents (the majority) indicated that it would not be acceptable (11 said it would be somewhat acceptable and 5 said it would be very acceptable).

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: [1]

- 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.

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

These findings were consistent with the responses in our 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.

In our 2017 Survey, 42% of HER2+ metastatic patients indicated that the cost of prescription medications had a significant or some impact on their treatment decision-making and quality of life.

Other financial barriers that metastatic breast cancer patients mentioned include: not qualifying for insurance at work, inability to change employers due to loss of insurance, and the prohibitive cost of new treatment options.

> *"Many of the next step treatments are very expensive [and not covered by government programs] and it is a HUGE struggle to get [coverage]. […] When dealing with an incurable disease the last thing you want to have to do is spend time on a letter writing campaign to argue about whether or not you should receive the drugs [recommended by your physician]. At about $1500.00 a week, I don't know many who can afford that."*
> "*Always a concern as you never know if the next drug will be covered or how long it takes to get approval from private coverage. Many times it delays treatment and this weighs on one's mind"*

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 the 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.

Patient Willingness to Tolerate Risk

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

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

Need for Personal Choice

What was revealed in the responses to the open ended question, and which was confirmed in the key informant interviews, is that it is imperative that women with metastatic breast cancer have access to, and the option of what drugs they take. 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. Metastatic breast cancer patients expressed the need for personal choice and autonomy in our 2012 Survey as well as in the 2017 Survey:

> *"I think patients (ESPECIALLY young patients) should be given more decision making power in terms of access to radical treatments to control disease. […] With two small I am determined to access any treatment that can extend my life and I hate struggling with doctors for this access." – 2012 Survey*
> *"I believe that I would prefer to tolerate severe restrictions in the quality of my life, if it meant that I would be able to have a longer period without progression." – 2012 Survey*
> *"It would be nice to have more choices and more information about them. I was lucky to get on a clinical trial perhaps because my oncologist was a research oncologist and involved in many. While I knew friend and acquaintances that had Stage IV BC and never informed of clinical trials, and sadly several did not survive the disease." – 2017 Survey*
> *"Accessibility to new drugs- not limiting choices." – 2017 Survey*
> *"Complete access to drug treatment choices and trials." – 2017 Survey*

5. Improved Outcomes

For metastatic patients, extension of progression-free survival (PFS) is of critical concern. Like any other treatment for metastatic breast cancer, patients have an expectation that tucatinib **(Tuksya)** will extend their progression-free survival with good quality of life when first- and second-line therapies stop working.

The HER2CLIMB trial evaluated tucatinib used in combination with trastuzumab and capecitabine in patients with HER2+ metastatic breast cancer who had been previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine. The HER2CLIMB trial showed that at 1 year, tucatinib used in combination with trastuzumab and capecitabine had an estimated PFS of 33.1%, compared to a PFS of 12.3% in the placebo group which administered only trastuzumab and capecitabine. The median length of duration for tucatinib in combination with trastuzumab and capecitabine was 7.8 months compared to 5.6 months for the placebo group. The risk of progression or death was 46% lower in the tucatinib-combination group compared to the placebo-combination group.

At 2 years, overall survival (OS) was 44.9%, with a median duration OS of 21.9 months for the tucatinib-combination group and 22.6% with a median duration OS of 17.4 months in the control group.

For patients with brain metastases receiving the tucatinib-combination, the estimated PFS was 24.9% with a median length of PFS of 7.6 months at 1 year. For those in the control group, estimated PFS was 0% and the median duration of PFS was 5.4 months.

Adverse Effects
The HER2CLIMB trial showed that tucatinib used in combination with trastuzumab and capecitabine was well tolerated by patients. Commonly reported side effects included: diarrhea, palmar–plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Most of these adverse effects were of grade 1 or 2.

Patients that were interviewed by CBCN shared that while they had side effects from tucatinib, they were minimal and manageable. Patient 1 shared that her only new side-effect from tucatinib was an itchy rash on her stomach which was easily treated with a cream. Patient 2 experienced fatigue and an upset stomach, both of which were easily treated. Both patients revealed that the side-effects from tucatinib were much more preferable to the side effects they had experienced on other treatments and therapies.

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. When living with no or with minimal cancer-related symptoms, and with minimal side effects from the treatment, patients are able to reduce the impact of cancer on their ability to care for children and dependents, continue with their employment and earn income, spend time with loved ones and participate in their life in a meaningful way by engaging in social activities, travelling, maintaining friendships, and pursuing personal interests.

The patients we interviewed on tucatinib indicated that tucatinib did not negatively impact their quality of life and they have both been able to maintain their lifestyle taking care of their home and family and travelling. Tucatinib has been a much more preferable treatment compared to other treatments such as chemotherapy.

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 advanced disease will progress with worsening symptoms until death, and embrace opportunities to try new treatments, even if benefits may be as little as a six month extension of progression-free disease. It is also very important for patients to have good quality of life when receiving treatment for metastatic disease. Patients that we speak to on a regular basis acknowledge the importance to have the energy to attend their children's activities and to spend time with family and friends. Our interviewees expressed the importance of what having access to tucatinib means to them and their family:

"I'm hoping it means a long life and grandkids. I'm hoping it will keep all the other tumours away for a significant amount of time. I understand that with metastases, it can

come back at any time, but we're hoping that tucatinib will provide a long life so we can see our kids grow up together."

6. Experience With Drug Under Review

Patient Profiles:
CBCN connected with two Canadian patients with different levels of experience with the treatment:

PATIENT 1: Is 36 years old and was diagnosed with DCIS and microinvasion in October 2018. In March 2020, she was diagnosed with HER2+ and HR- metastatic breast cancer with brain metastases. She is accessing this treatment through her private insurance; it is the only drug that her private insurance would cover. She has previously been treated with chemotherapy (Capecitabine), Herceptin, radiation, mastectomy, and Neratinib. She also underwent stereotactic radiosurgery.

PATIENT 2: Is 46 years old and was diagnosed with stage 1 HER2+ estrogen positive breast cancer in March 2013. In 2017, she was diagnosed with HER2+ metastatic breast cancer with lung, lymph nodes and rib metastases. She first accessed this treatment through a clinical trial. She has previously been treated with radiation,

The Impact of the Treatment on the Disease

Both patients expressed their personal satisfaction with the treatment.

"I didn't know if I was receiving the placebo or the drug but after a few cycles, based on my body's response, we knew that I was receiving the drug."

"It showed a [response] after only one treatment where my persistent cough subsided and I could take […] deep breathes again. I had more energy."

"My last MRI showed a decrease in the swelling that was originally around the tumour, and nothing else has shown up, so I guess it's doing its job really well."

While Patient 2 seemed to respond well to tucatinib when she began it, she did mention that after about 6 months, the impact began to slow down.

"It was excellent and remained excellent until May 2020 when breathing became a little more difficult as the lungs keep progressing. […] I can sit still and carry on a conversation without oxygen."

"It showed a response with shrinking the tumors in my lungs by a marked difference for a period of 6 months. At the 6 month scan, we noticed that things stopped shrinking and became with static or started growing slightly again. This meant we needed to switch up to ne different drug that would hopefully confuse the cancer once more and buy us more time until another trial or targeted therapy became available."

Assessing Risks Associated with the Treatment
Both patients expressed that they found the side effects to be very minimal as well as very manageable. Although Patient 1 experienced diarrhea, dry hands and feet, and mouth ulcers, she explained that she had these side-effects prior to being on tucatinib. The only new side-effect that she experienced while on tucatinib was an itchy rash on her stomach which went away after a week after using an antihistamine cream. She explained that this side-effect was much more tolerable than what she experienced when just using capecitabine.

Patient 2 shared that the side effects from tucatinib were mild and manageable, especially when compared to other side-effects that she has experienced from other treatments and therapies. She also expresses that no side-effect is too great for the extension of life that she is able to get with this treatment.

“Some of the side effects are gruelling and awful, [especially] the first few lines of treatment that can [cause] damage to your nerves and a condition called neuropathy which I [struggle] with today. I could not hold my infant for long periods as my hands would become numb and there was a risk of dropping her. Tucatinib had mild side effects. Fatigue is foremost with some stomach upset which is easily treated with meds.”

“There was nothing not acceptable to me. They were mild based on all of the other lines experienced and it’s a small [price] to pay for the extension of life.”

Alternatives to the Treatment
Both patients mentioned that tucatinib is a much more preferable option compared to other treatments that they have used and to other options that they have. Patient 2 especially stressed that the side effects from other treatments and therapies make tucatinib much more preferable. Patient 1 mentioned that without this treatment, she would be on neratinib.

“That is what they had me on originally before the tucatinib became available. So I guess if the tucatinib wasn’t there, we would have to go back to that. I was only on it for a few months, and it was so early in the diagnosis that it’s hard to say if it did much. It’s so hard to say. We had the surgery and they were concerned about the swelling at the beginning, but that eventually went down, especially after the tucatinib, so I think the tucatinib was the wiser choice to do when we had that available to us.”

Patient 2 mentioned that without this treatment, she would have to look at other chemotherapy options, as that is all that is available, she would have explored clinical trials available close to her, or she would have look at what other treatments are on the provincial formularies that she could have access to.

“Tucatinib is an definite advancement in the treatment of MBC and proves to extend life by some measure.”

The Social and Financial Impact of the Treatment

Patient 1 did not discuss the financial impact of the treatment. Patient 2 has had to go to Buffalo to access the American version to tucatinib at $26,000 per infusion. Travelling to have 15 more months of life with her family is worth it, but being on long-term disability, this is not feasible.

In terms of the social impacts of tucatinib, both patients discuss the impact that access to tucatinib has had on their quality of life and ability to be productive. Patient 1 expressed that she has been able to maintain her regular lifestyle with no interruption from being on tucatinib.

"I have been able to function completely normal. If you were to look at me, you wouldn't know anything was wrong, so I guess that's a good thing."

"Tucatinib hasn't affected my lifestyle at all, besides having to get up early to take my pills with breakfast. Sleeping in doesn't happen anymore."

Despite having the cancer metastasize to her lungs, patient 2 has been able to maintain a good quality of life on this treatment. She has had to reduce some of the work she does around the house but she expressed the importance of being able to spend every possible moment with her family.

"[…] I am now on oxygen and can only walk short distances so I sit outside and watch them play and [ride] their bikes as always. Just being with my family in any small moment is extraordinary to me.

7. Companion Diagnostic Test

Not applicable

8. Anything Else?

Not applicable

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH 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.

   CBCN did connect with the manufacturer, Seagen, to identify clinicians that could connect us with patients with experience on the treatment.

   All other research, interviews and outreach to patients was conducted independently by the Canadian Breast Cancer Network, as was the compilation of information and data for the writing of this submission.

   The Canadian Breast Cancer Network is committed to adhering to the Code of Conduct Governing Corporate Funding.

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. The Canadian Breast Cancer Network compiled and wrote this submission independently.

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.

4.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Seagen 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: Niya Chari
Position: Director of Health Policy and Public Affairs
Patient Group: The Canadian Breast Cancer Network (CBCN)
Date: March 26th, 2021

CADTH

CADTH Reimbursement Review
Patient Input Template

Name of the Drug and Indication	**Tucatinib: indicated in combination with trastuzumab and capecitabine for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine, separately or in combination.**
Name of the Patient Group	**CanCertainty**
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 CanCertainty Coalition is the united voice of more than 30 Canadian patient groups, cancer health charities, and caregiver organizations from across the country, joining together with oncologists and cancer care professionals to significantly improve the affordability and accessibility of cancer treatment.

For more information about the CanCertainty Coalition, please visit: https://www.cancertaintyforall.ca/

2. Information Gathering

Tucatinib is indicated for patients with HER2-positive breast cancer who have progressed on previous treatments. As an orally administered oncology drug, tucatinib is not automatically funded by certain provincial governments. In Ontario and the Atlantic provinces, only individuals over the age of 65 are automatically covered for oral oncology drugs.

The goal of our data collection efforts was to estimate the number of yearly HER2-positive breast cancer cases that develop brain metastases among the under 65 population, who do not have private or automatic public prescription drug coverage.

While tucatinib is indicated for patients both with and without brain metastases, we focused our information gathering on patients with brain metastases. Effective treatment of brain metastases remains an unmet clinical need for patients with breast cancer. Young age (<40) is a risk factor for brain metastases among HER2 patients[1], which is important to our efforts as an advocacy group for patients

[1] Maurer, C., Tulpin, L., Moreau, M., Dumitrescu, C., de Azambuja, E., Paesmans, M., … Awada, A. (2018). Risk factors for the development of brain metastases in patients with HER2-positive breast cancer. ESMO Open, 3(6), e000440. doi:10.1136/esmoopen-2018-000440

under 65. If approved, tucatinib could be a crucial drug for young breast cancer patients who have exhausted their other treatment options.

HER2-positive status is defined as HER2 protein overexpression in the cell, representing approximately 20% of all breast cancer cases. HER2 receptors are essential for cell proliferation, differentiation, and survival, and overexpression promotes aggressive growth of cancer cells[2]. Between a quarter and a half of the HER2-positive patients will die as the cancers metastasize to the brain. This is due to several factors: the prolonged survival of patients treated with first and second line anti-HER2 therapy, allowing for more time for brain relapse; the limited ability of anti-HER2 therapies to cross the blood-brain barrier; and inherent biological factors, such as visceral metastases.

A series of retrospective chart reviews tracked the percentage of HER2-positive patients that developed brain metastases. The percentages ranged from 25-48%[3]. For the purpose of this patient input submission, we estimated that the number of Canadian HER2-positive breast cancer patients who would develop brain metastases to be 30%. This percentage will serve our purpose of estimating the number of Canadians who would benefit by taking tucatinib.

Breast cancer incidence rates were sourced from the Canadian Cancer Registry (2017)[4]. They provide an breast cancer incidence rate for each five year age group in each province. We applied the age-specific incidence rates to the 2017 population demographics[5] of each province to arrive at the estimated new breast cancer cases each year by age and province. We chose to measure "potential financial toxicity" using data on lack of private drug coverage. The Canadian Life and Health Insurance Association[6] provides data on "extended health coverage." For each province, we extracted the percentage of individuals under the age of 65 without private drug coverage AND without automatic public drug coverage. These province-specific percentages were applied to the HER2-positivity and brain metastases rates to arrive at the final estimation: *the number of yearly HER2-positive breast cancer cases that will develop brain metastases among the under 65 population without private or automatic public prescription drug coverage.*

Limitations

We calculated these estimates to highlight an issue, not to be absolutely precise.

- The estimation of 30% of HER2-positive patients developing brain metastases is just that, an estimation. The epidemiology on brain metastases in this group is not rigorous. This percentage was estimated from a series of retrospective studies that used incomplete pharmacy records as data sources. Brain metastases are not always identified in breast cancer patients.
- Just because someone younger than 65 does not have private insurance does not mean that they are without financial support for their oral oncology medication. In each province, multiple programs exist to support individuals with high drug costs. Based on our experience as a patient advocacy group, we made the assumption that individuals with private health insurance incur less cost when prescribed oral oncology drugs.

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[2] Duchnowska, R., Lo bl, S., & Jassem, J. (2018). *Tyrosine kinase inhibitors for brain metastases in HER2-positive breast cancer. Cancer Treatment Reviews, 67, 71–77.* doi:10.1016/j.ctrv.2018.05.004

[3] Lin, N. U., & Winer, E. P. (2007). *Brain Metastases: The HER2 Paradigm. Clinical Cancer Research, 13(6), 1648–1655.* doi:10.1158/1078-0432.ccr-06-2478

[4] Statistics Canada. Table 13-10-0111-01 Number and rates of new cases of primary cancer, by cancer type, age group and sex. DOI**:** https://doi.org/10.25318/1310011101-eng

[5] Statistics Canada. (2017) *Annual Demographic Estimates: Canada, Provinces and Territories* [Data Visualisation Tool]. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1710000501

[6] Sutherland, Greg, and Thy Dinh. *Understanding the Gap: A Pan-Canadian Analysis of Prescription Drug Insurance Coverage*.

- The information on the number of Canadians who have progressed on first and second line therapies is not available. As tucatinib is indicated for patients both with and without brain metastases, we may be underestimating the true number of young Canadians who will indicated for tucatinib each year by focusing on brain metastases. However, this estimate still serves our purpose of highlighting that each year many young Canadians will be at risk of financial toxicity due to their disease.

Each year, we estimate that 1,231 HER2-positive breast cancer patients will be develop brain metastases.

Of these 1,231 cases, 641 will be under the age of 65. Depending on where these individuals live, their oral oncology medication may or may not be covered by the provincial government. For the 251 patients under 65 living in British Columbia, Alberta, Saskatchewan, and Manitoba oral oncology medication is automatically covered. Residents of Ontario and the Atlantic provinces under the age of 65 are not automatically covered under public pharmacare plans. Their route to treatment access is not simple. By out estimations, 50 of these Ontario cancer patients (under the age of 65) will not have private health insurance. Before they can receive their medication these patients will have to navigate a complicated process of funding applications, approval delays, locating a pharmacy, and waiting for their prescription to be filled/delivered. They will incur out-of-pocket costs and a sizeable portion of their income will go towards their medication.

Assuming tucatinib is ultimately funded by the provinces and territories, the following chart details the number of patients in each province/territory that would be face financial barriers in accessing this treatment:

	Breast cancer diagnoses per year[i]		HER2-positive[ii]		Brain metastases[iii]		Without private drug coverage	
	Over 65	Under 65	Over 65	Under 65	Over 65	Under 65	Over 65	Under 65
Canada[v]	9,831	10,685	1,966	2,137	590	641	0	57
BC	1,694	1,768	339	354	102	106	0	0
AB	1,329	1,612	266	322	80	97	0	0
SK	401	356	80	71	24	21	0	0
MB	429	439	86	88	26	26	0	0
ON	4,945	5,592	989	1,118	297	335	0	50
NB	340	306	68	61	20	18	0	4
NS	418	338	84	68	25	20	0	2
PE	51	61	10	12	3	4	0	1
NL	225	212	45	42	13	13	0	0

(i) Estimated from province and age-specific incidence rates from Stats Canada for the year 2017
(ii) HER2 overexpression occurs in approximately 20% of breast cancer cases
(iii) Brain metastases occur in at least 30% of HER2 positive breast cancer cases
(iv) Excluding Quebec (who do not report cancer cases in the same manner) and the territories (for whom we do not have health insurance data)

3. Disease Experience

Access problems can be so difficult that in many hospitals and cancer centres across Canada, such as those in Ontario, a new type of social worker known as a *drug access navigator* has been established (and funded) to assist patients and clinicians navigate the byzantine treatment access structures. In Ontario, the organization that supports these navigators is known as the Oncology Drug Access Navigators of Ontario (ODANO). They describe the problem that their association works to resolve as follows: *Drugs are an important part of cancer treatment, yet patients often have difficulty accessing coverage for the most effective medicines. The complexity of cancer drug coverage in Canada can overwhelm patients and families.*

And

For example, although cancer drugs administered in hospitals and clinics are often offered free of charge to patients, half of all new cancer drugs are taken at home and, therefore, many are not covered by the public health system. Unfortunately, many of our patients do not have any private insurance. If a patient is fortunate enough to have private coverage, many drug plans require a 20% co-payment, which can quickly become a financial burden to patients on expensive medications.

British Columbia, Alberta, Saskatchewan, Manitoba, Quebec, NWT, Yukon, and Nunavut cover the reimbursement of oral cancer drugs for all in need. Ontario and the Atlantic provinces do not.

In Ontario and Atlantic provinces, with respect to access to approved cancer treatments, there is institutional discrimination against those who are young, uninsured and who have cancer requiring take-home cancer treatment. With 60% of all new cancer drugs being developed with oral formulations, this issue urgently needs to be resolved through policy change. Traditionally, cancer treatments were administered to patients by an IV in the hospital. Over the past 15 or so years, an increasing number of effective cancer treatments can be taken at home by pill or injection. Take-home cancer medications are now a fundamental part of today's cancer treatments and should be recognized equally within our health care systems. Patients requiring an intravenous treatment can start that medication as soon as needed and don't face any financial or administrative burdens provided the drug is included on the provincial formulary.

However, when take-home cancer medications are prescribed, patients in Ontario and the Atlantic provinces, who are under 65, and lack adequate private insurance, have to apply to a variety of funding assistance programs and ultimately pay a significant deductible or co-pay from their personal savings. In some cases, the cost to the patient might be as high as $23,400 annually, based upon Nova Scotia's Family Pharmacare Program. To qualify for assistance programs, patients and their families have to submit significant amounts of personal and financial information and often face weeks of stressful delay in starting their cancer treatment - until the paperwork and approvals are resolved.

Even for patients with private drug insurance, the reality is that many face significant co-pays, deductibles or annual/lifetime caps. For example, some private insurance plans have a cap of $2,000 for prescription drugs for the entire year. The majority of take-home cancer drugs cost more than $20,000 per year. Two-tiered pharmacare in Ontario and the Atlantic Provinces discriminates on the basis of age, income, geography, cancer type, and cancer treatment, and is financially ruining many lives.

A survey[7] of over 1,600 Nova Scotians, commissioned by the CanCertainty Coalition, demonstrates that drug coverage for cancer patients is a serious and growing problem.

- More than half (57 percent) of Nova Scotians expect the provincial health care system will pay for take-home cancer medications. In reality, patients will ultimately pay a significant deductible or co-pay from their personal funds.

[7] Strategic Directions. *Cancertainty & Strategic Directions IVR Report*. 2017. Available at: https://d3n8a8pro7vhmx.cloudfront.net/cancertainty/pages/119/attachments/original/1490212245/CanCertaintySurvey_October2016.pdf

- Three out of five people in Nova Scotia (60 percent) said they would consider leaving the province if faced with having to pay for their cancer drugs. Only seven percent could afford monthly drug costs of over $200.

4. Experiences With Currently Available Treatments

Take-home cancer drugs (THCD) are medications used for the active treatment of cancer and are usually dispensed for administration in the home (e.g., oral chemotherapy). These drugs have become a standard treatment for many cancers and present opportunities for patients, providers, and the health system. However, flaws in our current drug coverage system result in some patients not being able to access these treatments.

The term "financial toxicity" describes the distress and hardship arising from the financial burden of cancer treatment. Even in counties with government funded universal healthcare, financial toxicity is an issue for cancer patients and their families. Financial toxicity comes in many forms: out of pocket costs, lost income, travel expenses etc. Patients may deal with their financial burden by delaying or foregoing care. They may take less medication than prescribed, utilize over-the-counter drugs in place of prescribed medications, decline procedures, and skip appointments in an attempt to defray costs. The combination of high drug prices, particularly of oral targeted anticancer drugs, and increased cost sharing has made patients more vulnerable to medication non-adherence. Patients who are younger, have lower income, and are uninsured appear to be at greater risk of medication non-adherence. Although government funded public healthcare exists in many very high development index countries, financial toxicity is still common among cancer patients and caregivers. The evidence suggests that those with a shorter time since diagnosis, not currently working, and with more severe cancers have higher rates of financial toxicity, including stress and strain[8].

An unfunded oral oncology drug is financially toxic compared to a funded IV oncology drug. The disease experience of cancer patients that require oral drugs is a dual track of disease and economic hardships. After receiving their diagnosis, deciding on a medication, and dealing with the side effects, patients in Ontario and the Atlantic provinces have to consider the financial side of their diagnosis. *"Hearing that you have cancer is devastating. Finding out that you can't pay for the medication that will make you well is catastrophic. It doesn't have to be this way"* ([redacted], Ontario).

The financial side of cancer treatment is unnecessarily burdensome. *"When you are going through any kind of sickness, whatever the severity of it, the last thing you should have to worry about is your medication cost"* ([redacted], Ontario). In addition to dealing with cancer, and not being well enough to work, patients in Ontario and the Atlantic provinces spend days on end, sometimes months, wading through paperwork in order to get approval for coverage of the oral chemotherapy that has kept them alive. Because some cancer treatments are not automatically funded, treatment is delayed for many patients. They wait weeks for government approval before dealing with insurance companies and pharmacies to receive their prescription. Patients often pay out of pocket for the first few weeks of their treatment, which they may not be reimbursed for. *"My doctor prescribed a new drug that is not covered by the government therefore I had to find insurance to cover it which costs around $5000.00 a month, I came up with insurance to cover it but I had to pay the pharmacy first then the insurance would reimburse me some time later. My problem I do not have the $5000 to pay out let alone wait till they reimburse me"* ([redacted], Ontario).

"Cancer isn't fair, but access to treatment should be!" ([redacted], Ontario).

[8] Longo, C.J., Fitch, M.I., Banfield, L. *et al.* Financial toxicity associated with a cancer diagnosis in publicly funded healthcare countries: a systematic review. *Support Care Cancer* **28,** 4645–4665 (2020). https://doi.org/10.1007/s00520-020-05620-9

5. Improved Outcomes

N/A

6. Experience With Drug Under Review

CanCertainty's focus for this submission is on issues related the distress and hardship arising from the financial burdens associated with cancer treatment. If tucatinib were to be reimbursed for patients with HER2-positive breast cancer who have progressed on previous treatments, there would be some patients under 65 in Ontario and Atlantic Canada that would face significant financial and administrative barriers in accessing treatment.

7. Companion Diagnostic Test

N/A

8. Anything Else?

Equitable Access

We recommend that pCODR, when assessing and reporting on implementation issues with respect to Osimertinib for NSCLC, examine the issues of equitable access across all Canadian jurisdictions.

Safety

With respect to implementation, we believe pCODR should also examine the issue of safety with respect to take-home cancer drugs. From 2006 to 2001, it is estimated that Ontario's computerized provider entry system, the *Oncology Patient Information System* (OPIS) prevented 8,500 adverse drug events, 5,000 physician office visits, 750 hospitalizations, 57 deaths, and saved millions in annual healthcare costs. But, this system is only used for only IV Drugs[9]. As a result, patients requiring take-home cancer drugs (THCD) in Ontario are (currently) subject to significant safety challenges, and health systems are subject to significant annual costs (physician office visits, hospitalizations etc).

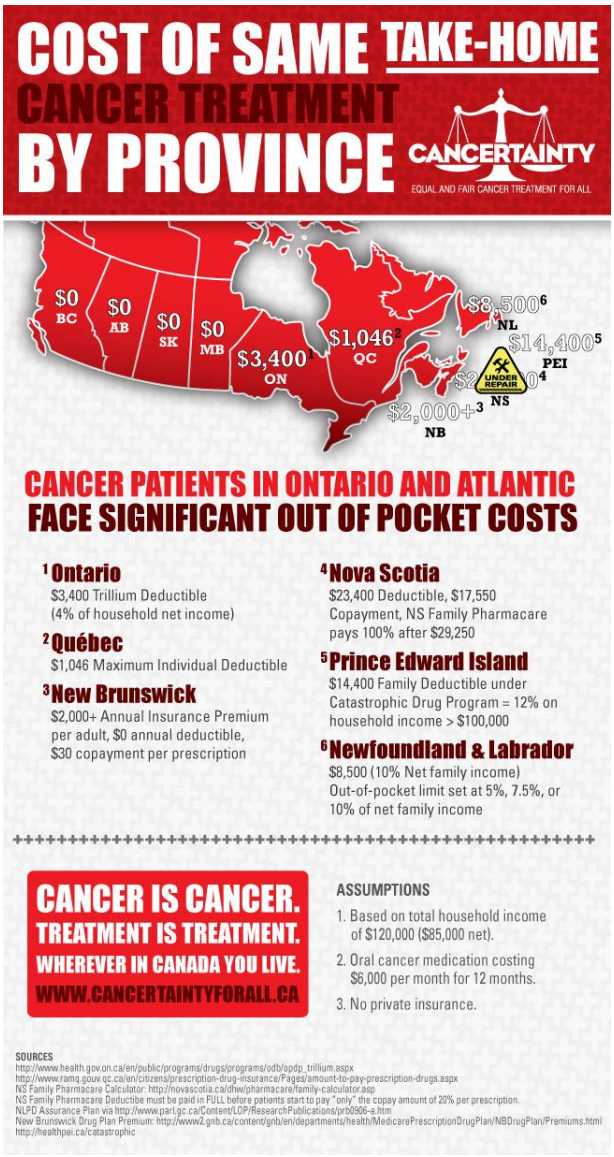
In Ontario, dispensing and delivery models for THCD have been documented to be inconsistent and pose serious safety concerns for patients and their families. Some patients receive their medication from hospital pharmacies, some from specialty pharmacies, and some from community pharmacies that lack specialization and training in the handling of toxic cancer medications. This contrasts with the robust guidelines and clear processes that have been developed for intravenous cancer drugs (IVCD) where delivery is more comprehensive, organized, safer and patient-centred than THCD. There are numerous known safety and quality deficits related to the current method of community dispensing of THCD including incorrect dosing and handling, limited monitoring and non-adherence (which can lead to under or overdosing), serious toxicity, morbidity, and mortality. Patient lives and well-being are at stake. Ontario urgently needs to reform its systems for THCD dispensing that embed high-quality, safe practices that recognize the unique aspects of these drugs.

In April 2017, Cancer Care Ontario organized the Oncology Pharmacy Task Force with the mandate to advise Cancer Care Ontario (CCO) on how to enhance the current system for THCD delivery to optimize quality and safety; and subsequently, to deliver a report to the Ministry of Health and Long-Term Care (MOHLTC) based on the findings of the Task Force. The Task Force included representatives from patient advocacy groups, pharmacy and pharmacist associations, regulatory and standard setting organizations, and subject matter experts. On March 25th, 2019 the report was completed and published on the CCO website, **but there has been no follow up or action taken to the many important recommendations.** The report Enhancing the Delivery of Take-Home Cancer Drugs in Ontario (March 2019) can be found at:

https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/full/1_CCO_THCD_Report_25Apr2019.pdf

CanCertainty suggests that pCODR examine the issues of safety and dispensing when examining and reporting on issues concerning pan-Canadian implementation of Osimertinib for NSCLC.

[9] eHealth Ontario. *Cancer Care Ontario and eHealth Ontario Partner to Deliver Safer Chemotherapy Treatment.* Toronto, ON: 2011. Available at: https://ehealthontario.on.ca/en/news/view/cancer-care-ontario-ehealth-ontario-partner-to-deliver-safer-chemotherapy


COST OF SAME TAKE-HOME CANCER TREATMENT BY PROVINCE
CANCERTAINTY
EQUAL AND FAIR CANCER TREATMENT FOR ALL
$0 BC
$0 AB
$0 SK
$0 MB
$3,400 ON
$1,046 QC
$2,000+ NB
$8,500 NL
$14,400 PEI
NS
UNDER REPAIR
CANCER PATIENTS IN ONTARIO AND ATLANTIC FACE SIGNIFICANT OUT OF POCKET COSTS
[1] Ontario
$3,400 Trillium Deductible (4% of household net income)
[2] Québec
$1,046 Maximum Individual Deductible
[3] New Brunswick
$2,000+ Annual Insurance Premium per adult, $0 annual deductible, $30 copayment per prescription
[4] Nova Scotia
$23,400 Deductible, $17,550 Copayment, NS Family Pharmacare pays 100% after $29,250
[5] Prince Edward Island
$14,400 Family Deductible under Catastrophic Drug Program = 12% on household income > $100,000
[6] Newfoundland & Labrador
$8,500 (10% Net family income) Out-of-pocket limit set at 5%, 7.5%, or 10% of net family income
CANCER IS CANCER. TREATMENT IS TREATMENT. WHEREVER IN CANADA YOU LIVE.
WWW.CANCERTAINTYFORALL.CA
ASSUMPTIONS
1. Based on total household income of $120,000 ($85,000 net).
2. Oral cancer medication costing $6,000 per month for 12 months.
3. No private insurance.
SOURCES
http://www.health.gov.on.ca/en/public/programs/drugs/programs/odb/opdp_trillium.aspx
http://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance/Pages/amount-to-pay-prescription-drugs.aspx
NS Family Pharmacare Calculator: http://novascotia.ca/dhw/pharmacare/family-calculator.asp
NS Family Pharmacare Deductbe must be paid in FULL before patients start to pay "only" the copay amount of 20% per prescription.
NLPD Assurance Plan via http://www.parl.gc.ca/Content/LOP/ResearchPublications/prb0906-e.htm
New Brunswick Drug Plan Premium: http://www2.gnb.ca/content/gnb/en/departments/health/MedicarePrescriptionDrugPlan/NBDrugPlan/Premiums.html
http://healthpei.ca/catastrophic

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.

   This submission was completed exclusively using CanCertainty resources and personnel and contract personnel.

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.

Data was collected and analyzed using CanCertainty personnel/contract personnel.

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

Note: Seagen Canada Inc. has never provided financial support to CanCertainty.

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: Robert Bick
Position: Co-Lead
Patient Group: CanCertainty
Date: April 23, 2021

CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Tucatinib is indicated in combination with trastuzumab and capecitabine for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine, separately or in combination.**
Name of the Patient Group	**Rethink Breast Cancer**
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Rethink Breast Canada's mission is to empower young people who are concerned about and affected by breast cancer through education, support and advocacy. Since 2001, we have been building community for those diagnosed with breast cancer at a younger age, providing support and resources to help them live the best quality of life. We represent their voices and strive to ensure their needs and values are heard and considered in all aspects of breast cancer treatment and care at all stages of their breast cancer experience. Because up to 30% of all breast cancers become metastatic, Rethink Breast Cancer has always worked closely with young MBC patients. Our community experiences tremendous loss from this life-limiting disease and our organization places a major focus on the unmet needs of those living with MBC. www.rethinkbreastcancer.com

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.

Online patient surveys were conducted between March 2 and April 7, 2021. The survey asked questions about the impact of breast cancer on the lives of patients, the effect of current treatments and their willingness to accept side effects for improved health outcomes. The survey also included questions directed to patients with Tukysa treatment experience. Potential respondents were identified through messages to Rethink Breast Cancer's mailing list as well as the Rethink's closed Facebook group and partner organizations. Messages were also posted on Rethink's public Facebook, Instagram and Twitter channels as well as the Breastcancer.org, Cancer Connection and Cancer Survivors Network online discussion forums.

A total of 51 women completed the patient survey. Of these respondents, 37 are from Canada (representing Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Quebec & Saskatchewan), 12 are from the United States, 1 is from Mexico and 1 chose not to answer. All 51 respondents have been diagnosed with HER2-positive locally advanced unresectable or metastatic breast cancer, and 6 respondents have treatment experience with Tukysa. The latter group of patients will be profiled in section 6. Five of the respondents in this group agreed to participate in telephone interviews with Rethink staff members to discuss their treatment experience and elaborate on their feedback.

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?

7 respondents were diagnosed in 2020, 8 were diagnosed in 2019, 6 were diagnosed in 2018, 3 were diagnosed in 2017, 8 were diagnosed in 2016, 6 were diagnosed in 2015, 8 were diagnosed in 2014 and 5 were diagnosed earlier.

21 respondents are currently receiving first-line treatment, 5 are receiving second-line treatment, 9 are receiving third-line treatment or higher, 8 are receiving treatment after recurrence, 2 are under surveillance following treatment, 3 have no evidence of disease and 3 indicated that they are in a different phase of treatment.

14 respondents reported brain metastases from their breast cancer.

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).

All 51 respondents provided information about the medications they had undergone since their diagnosis. Trastuzumab and pertuzumab were by far the most common forms of treatment. Trastuzumab emtansine, capecitabine and paclitaxel were the only other medications reported by more than 4 respondents.

Medications Received	n	Medications Received	n
Trastuzumab (Herceptin)	49	Trastuzumab deruxtecan (Enhertu)	1
Pertuzumab (Perjeta)	45	Carboplatin (Paraplatin)	1
Trastuzumab emtansine (Kadcyla)	12	Vinorelbine (Navelbine)	1
Capecitabine (Xeloda)	10	Palbociclib (Ibrance)	1
Paclitaxel (Taxol)	9	Ribociclib (Kisqali)	1
Docetaxel (Taxotere)	4	Fulvestrant (Faslodex)	1
Trastuzumab, pertuzumab and trastuzumab emtansine	4	Pertuzumab, trastuzumab and hyaluronidase-zzxf (Phesgo)	1
Lapatinib (Tykerb)	3	Zoledronic acid (Zometa)	1
Nab-paclitaxel (Abraxane)	3	Abemaciclib (Verzenio)	1
Neratinib (Nerlynx)	2	Anastrozole (Arimidex)	1
Tamoxifen (Nolvadex)	2	Denosumab (Xgeva)	1
Eribulin (Halaven)	2	SYD985	1

Fatigue was the most commonly reported side effect of these treatments (86%, n=49), followed by diarrhea (71%), nausea (49%) and insomnia (45%).

Diarrhea and fatigue were most commonly cited by respondents as the most-difficult-to-tolerate side effects of these treatments. Nausea, loss of appetite, neuropathy, skin problems and breathing difficulties were also cited by multiple respondents.

A majority (69%, n=51) of respondents did not have difficulty accessing treatment. However, 22% reported that they were unable to access treatment because it was unavailable in Canada. 28% of respondents (n=50) also reported that they needed financial assistance due to the costs associated with breast cancer.

Some of the general comments about previous treatments include:

- Taxol reduced mets early in treatment. Herceptin, Perjeta continue to keep me stable. So far side effects are tolerable, but my quality of life has diminished.
- Xeloda is rough, feet are on fire constantly and hands hurt. Shortness of breath at times and weak. Will be 2 years in June. Herceptin seems to be fine - just get tired and I did well with the Perjeta.
- They all worked well for a while until I had to change. Abraxane caused neuropathy and heavy leg syndrome, Verzenio caused occasional diarrhea and even though I have had just one treatment of Eribulin, I feel more neuropathy and heavy leg syndrome.
- Grateful to have these targeted therapies.
- Targeted treatment has been a dream compared to all body chemo.

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?

Rethink Breast Cancer asked patients to evaluate the importance of different outcomes for their breast cancer treatment on a scale of 1 (not important) to 5 (very important). Respondents ranked all of the outcomes as important, but prioritized long-term health outcomes with 48 of 51 patients giving the highest score to controlling disease progression and 46 of 49 patients doing the same with preventing recurrence.

It may be worth noting that the respondents to this survey gave lower scores to reducing symptoms and managing side effects than metastatic breast cancer respondents from other surveys. This may reflect distinctive patient values for women with HER2-positive metastatic breast cancer. However, we should also allow that it may be a function of the limited sample size.

Importance of outcome	1 - not mportant	2	3	4	5 – very mportant	Average
Contro ng d sease	0.00% 0	1.96% 1	0.00% 0	3.92% 2	94.12% 48	4.90 51
Reduc ng symptoms	0.00% 0	5.88% 3	31.37% 16	19.61% 10	43.14% 22	4.00 51
Ma nta n ng qua ty of fe	0.00% 0	0.00% 0	0.00% 0	23.53% 12	76.47% 39	4.76 51
Manag ng s de effects	0.00% 0	6.00% 3	22.00% 11	24.00% 12	48.00% 24	4.14 50
Prevent ng recurrence	0.00% 0	2.04% 1	0.00% 0	4.08% 2	93.88% 46	4.90 49

Comments from respondents include:

- The ultimate goal is to maximise longevity and personally, I can tolerate many side effects if it means I can live longer.
- I just want to live.

Respondents were also asked to rate how much they would be willing to tolerate new side effects from therapies that can control disease profession. On a scale of 1 (will not tolerate side effects) to 10 (will tolerate side effects), the average score was 7.2 (n=49), suggesting a strong tolerance for side effects for therapies that can improve long-term health outcomes.

Rating	Responses	Rating	Responses
1	0.00% 0	6	10.20% 5
2	0.00% 0	7	14.29% 7
3	6.12%	8	22.45%

	3		11
4	0.00% 0	9	6.12% 3
5	6.12% 3	10	34.69% 17

Comments included:

- Being alive and staying alive is my goal.
- It's very hard on my quality of life but I want to live.
- I suffer daily to live for today and any other day that I'm blessed to have.
- I just want more time with my daughter and husband. I would tolerate anything for more time.
- I can adapt.

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?

Six respondents received Tukysa for treatment of HER2-positive locally advanced unresectable or metastatic breast cancer. Four of these respondents received Tukysa in combination with trastuzumab and capecitabine following prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine, separately or in combination.

- Patient A is from the United States. She was diagnosed in 2016 and is currently undergoing second-line treatment. She was shifted to the Tukysa-Herceptin-Xeloda combination to better treat her brain metastases. She has been receiving Tukysa for 3-6 months.
- Patient B is from Ontario. She was diagnosed in 2013 and is currently receiving third-line treatment or higher. She has been receiving Tukysa for less than three months.
- Patient C is from Ontario. She was diagnosed in 2017 and is currently receiving treatment after a recurrence. She has brain metastases. She received Tukysa for less than three months and was forced to discontinue treatment due to the side effects.
- Patient D is from Alberta. She was diagnosed in 2014 and is currently receiving third-line treatment or higher. She has brain metastases. She has been receiving treatment with Tukysa for less than three months.

One respondent did not receive Tukysa in combination with trastuzumab and capecitabine:

- Patient E is from the United States. She was diagnosed in 2018 and currently has had no evidence of disease for more than two years. She had brain metastases. She has been receiving Tukysa for 3-6 months. Her Tukysa dosage was lowered due to the side effects. She also has treatment experience with zoledronic acid and paclitaxel.

One respondent did not receive Tukysa in combination with trastuzumab and capecitabine or following prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine, separately or in combination.

- Patient F is from the United States. She was diagnosed in 2019 and is currently receiving third-line treatment or higher. She has brain metastases. She has been receiving Tukysa for 6-12 months. She was previously treated with paclitaxel, anastrozole, denosumab, zoledronic acid, a craniotomy as well as one session of high-dose radiation.

Treatment Experience

Patients were asked to rate the change to their quality of life on Tukysa compared to other therapies they had received on a scale of 1 (much worse) to 5 (much better). Respondents felt strongly that Tukysa helped control disease progression and prevented recurrence. The responses in other areas were generally close to neutral.

Change to qua ty of fe on Kadcy a	1 – much worse	2	3	4	5 – much better	Average
Metastat c cancer symptoms	0.00% 0	0.00% 0	40.00% 2	40.00% 2	20.00% 1	3.80 5
Drug s de effects	0.00% 0	16.67% 1	50.00% 3	16.67% 1	16.67% 1	3.33 6
Ma nta n ng qua ty of fe	16.67% 1	0.00% 0	16.67% 1	33.33% 2	33.33% 2	3.67 6
Contro ng d sease progress on	0.00% 0	0.00% 0	0.00% 0	40.00% 2	60.00% 3	4.60 5
Prevent ng recurrence	0.00% 0	0.00% 0	0.00% 0	20.00% 1	80.00% 4	4.80 5
Ab ty to work	20.00% 1	0.00% 0	40.00% 2	20.00% 1	20.00% 1	3.20 5
Ab ty to s eep	0.00% 0	16.67% 1	33.33% 2	33.33% 2	16.67% 1	3.50 6
Ab ty to dr ve	20.00% 1	0.00% 0	20.00% 1	40.00% 2	20.00% 1	3.40 5
Ab ty to perform househo d chores	33.33% 2	00.00% 0	16.67% 1	0.00% 0	50.00% 3	3.33 6
Ab ty to care for ch dren	33.33% 2	16.67% 1	16.67% 1	0.00% 0	33.33% 2	2.83 6

Comments include:

- I am feeling better than I previously was. It has helped to reduce symptoms. (Patient B)
- It's not bad at all. I've been on a lot of treatments and this one isn't so bad. (Patient D)

Side Effects

Diarrhea was the most commonly reported side effect of Tukysa (5 of 6 respondents). Decreased appetite, fatigue, nausea, hand-foot syndrome were also reported by multiple respondents.

When asked how much they could tolerate the side effects associated with Kadcyla on a scale of 1 (completely intolerable) to 10 (completely tolerable), the average rating was 7. However, this represented a divided response. Patients C and F gave scores of 1 and 3 respectively, while all other respondents gave scores of 8 or higher.

Patient comments included:

- Initially, side effects of nausea, vomiting and diarrhea were bad but with the right meds to control that, I'm doing really well and feel great. (Patient A)
- Side effects are manageable. Some mild diarrhea at the beginning, but managed with some Imodium. (Patient B)
- This drug was horrible for me. Side effects not tolerable at all. Mind you, no dose reduction was suggested either. Not sure I would have done them.(Patient C)

Treatment Options

Chemotherapy was the only alternative treatment suggested if Tukysa was unavailable.

Patients also reflected on the importance of having a treatment option for brain metastases:

- It's a huge relief that we're making progress in treating brain mets because right now, that's the thing that's liable to take me down. (Patient A)
- I was happy. We were all happy to find out that I had an option. (Patient D)
- At least giving people the opportunity to make the decision is critical. Everyone should have the choice to try it or not. (Patient E)

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.

8. Biosimilar

If the drug in review is a biosimilar (also known as a subsequent entry biologic), please outline any expectations or concerns held by patients, caregivers, and families about the biosimilar. If the biosimilar

was less expensive than the brand name drug, what would the impact be for patients, caregivers, and families?

9. Anything Else?

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

Recommend Tukysa: When asked if they would recommend Tukysa to other patients with breast cancer, five patients said that they would. Patient C was the sole dissenter.

Asked to elaborate, respondents commented:

- Is very tolerable so far and seems to be working. The effectiveness with brain mets is especially important and I am hopeful. (Patient A)
- So far so good. Cancer is stable based on last scan. Hopeful that this can continue. (Patient B)
- Side effects are horrible (Patient C)
- I don't mind as long as it keeps me alive. I don't like how much pills I have to take. (Patient D)
- Absolutely fantastic drug. As an attorney/freelance medical editor, nothing was more devastating than learning that my brain has been affected. I don't care how I look; I don't care if I am fatigued or bloated or have painful hands...I am my brain, and my ability to conduct complex analysis. I wish I could personally thank every researcher involved in the design of this drug, and any drug with the capacity to cross the blood/brain barrier. (Patient E)
- I'm glad that I have the opportunity to take Tukysa. I feel that it's extending my life. (Patient F)
- 100% - it is a Life-saver for me. Feeling healthier and able to go back to my routine. (Patient B)
- While I see from the comments posted by others taking Tukysa that some people experience side effects that they feel are intolerable, the fact that this formulation permits access to the brain is a game-changer and should encourage anyone with the ability to access it to try it. In the event that side effects are, in fact, intolerable, thereby dictating a medication switch, Tukysa should be initially approached as an opportunity. As Canadians will well understand, "You miss 100% of the shots you don't take." (Patient E)
- Hopefully, it gets approval worldwide. (Patient A)

Key Points:

1. All respondents agreed that Tukysa helped to control disease progression and prevent recurrence compared to other therapies that they had received.
2. Breast cancer patients prioritize long-term health outcomes and are usually willing to tolerate side effects from therapies that can control disease progression.
3. There are no drugs currently indicated for treatment of brain metastases.

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 asked Seattle Genetics to provide us with information about the general characteristics of the drug and it's benefits. We asked our Scientific Advisory Committee (medical oncologists) about this drug and it's benefits and whether it addressed an unmet need. Adam Waiser is a freelance health technology assessment writer who we contracted to help us with writing 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.

   We contracted Adam Waiser to help us develop the survey we used to collect the data used in this submission. All interviews were conducted by Rethink Breast Cancer staff. Adam Waiser helped us analyze the findings of our survey and interviews.

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
Seagen 2020			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: MJ DeCoteau
Position: Executive Director
Patient Group: Rethink Breast Cancer
Date: April 19, 2021