CADTH

## CADTH Reimbursement Review

# Patient Input

### ZANUBRUTINIB (Brukinsa)

(BeiGene Canada ULC)

**Indication:** Waldenström's macroglobulinemia

**CADTH received patient input from:**

CanCertainty

Lymphoma Canada (LC), Canadian Organization for Rare Disorders (CORD), Waldenstrom Macroglobulinemia Foundation of Canada (WMFC)

**May 14, 2021**

CADTH

# CADTH Reimbursement Review
# Patient Input Template

| | |
|---|---|
| **Name of the Drug and Indication** | **Zanubrutinib: for the treatment of patients with Waldenström's macroglobulinemia** |
| **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

Zanubrutinib is indicated for patients with Waldenstöm's macroglobulinemia. As an orally administered oncology drug, zanubrutinib 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 medication. For the small number of Waldenstöm's macroglobulinemia patients under 65 living in these provinces, their diagnosis could lead to severe economic hardships. However, if zanubrutinib is fully funded by all provinces, these patients will instead be able to focus on their treatment and spending time with their family and friends.

Our data collection efforts aimed to estimate the number of patients who are at risk of severe financial burden as a result of their diagnosis. We calculated the number of Waldenstöm's macroglobulinemia cases in Canada each year among the under 65 population who do not have private or automatic public prescription drug coverage.

Waldenstöm's macroglobulinemia is a (rare) type of non-Hodgkin lymphoma (NHL) where the cancer cells make large amounts of an abnormal protein (called a macroglobulin). We estimate that about 217 Canadians are diagnosed with this disease each year. Of these 217 cases, 68 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 21 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 plans. Their

route to treatment access is not simple. By out estimations, 4 of these Ontario cancer patients 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 medication in the mail. They will incur out-of-pocket costs and sizeable portion of their income will go towards their medication. This is a small number of patients.

Waldenstöm's macroglobulinemia incidence rates were sourced from Yin et. al. (2020)[1]. They provided incidence rates for each 10 year age group. We applied the age-specific incidence rates to the 2017 population demographics[2] of each province to arrive at the estimated number of new Waldenstöm's macroglobulinemia 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[3] 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 Waldenstöm's macroglobulinemia case rates to arrive at the final estimation: *the number of yearly* Waldenstöm's macroglobulinemia cases *among the under 65 population without private or automatic public prescription drug coverage.*

Assuming zanubrutinib 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:

| | **Population[i]** | | **Cases of Waldenström macroglobulinemia[ii]** | | **Without private drug coverage[iii]** | |
|---|---|---|---|---|---|---|
| | **Over 65** | **Under 65** | **Over 65** | **Under 65** | **Over 65** | **Under 65** |
| **Canada[iv]** | 6,135,028 | 30,410,267 | 149 | 68 | 0 | 5.0 |
| BC | 986,936 | 4,160,776 | 24 | 10 | 0 | 0 |
| AB | 610,974 | 3,810,902 | 15 | 7 | 0 | 0 |
| SK | 191,020 | 987,661 | 5 | 2 | 0 | 0 |
| MB | 221,666 | 1,157,597 | 5 | 2 | 0 | 0 |
| ON | 2,594,358 | 12,139,656 | 63 | 27 | 0 | 4.0 |
| NB | 171,262 | 610,214 | 4 | 2 | 0 | 0.3 |
| NS | 208,825 | 770,526 | 5 | 2 | 0 | 0.2 |
| PE | 31,957 | 127,668 | 1 | 0 | 0 | 0.1 |
| NL | 116,228 | 405,875 | 3 | 1 | 0 | 0.0 |

(i) From Stats Canada for the year 2017 to align with incidence calculations.
(ii) Age-specific incidence rates were sourced for all age groups (10 year increments). In
(iii) Province specific private drug coverage rates provided by The Canadian Life and Health Insurance Association.
(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).

[1] Yin, X., Chen, L., Fan, F., Yan, H., Zhang, Y., Huang, Z., … Hu, Y. (2020). Trends in Incidence and Mortality of Waldenström Macroglobulinemia: A Population-Based Study. Frontiers in Oncology, 10. doi:10.3389/fonc.2020.01712
[2] 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
[3] Sutherland, Greg, and Thy Dinh. *Understanding the Gap: A Pan-Canadian Analysis of Prescription Drug Insurance Coverage*.

**Limitations**

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

- 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.
- The incidence rates were not sourced from a Canadian population. Differing demographics across the provinces may skew the actual case counts.

## 3. Disease Experience

The access problems are 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[4]: *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

[4]https://odano.ca/

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[5] 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.
- 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[6].

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*

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

[6] 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

*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).

## 5. Improved Outcomes

## 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 zanubrutinib 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 zanubrutinib, 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[7]. 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

[7] 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

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 zanubritinib.

# COST OF SAME TAKE-HOME CANCER TREATMENT BY PROVINCE

CANCERTAINTY
EQUAL AND FAIR CANCER TREATMENT FOR ALL


## 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

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**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 Deductibe 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 |
| AstraZeneca | | | 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: Robert Bick
Position: Co-Lead
Patient Group: CanCertainty
Date: May 14, 2021

CADTH

# CADTH Reimbursement Review
# Patient Input Template

| | |
|---|---|
| **Name of the Drug and Indication** | **Zanubrutinib, Waldenström's macroglobulinemia** |
| **Name of the Patient Group** | **Lymphoma Canada (LC), Canadian Organization for Rare Disorders (CORD), Waldenstrom Macroglobulinemia Foundation of Canada (WMFC)** |
| **Author of the Submission** | [redacted] |
| **Name of the Primary Contact for This Submission** | [redacted] |
| Email | [redacted] |
| Telephone Number | [redacted] |

## 1. About Your Patient Group

Lymphoma Canada is a national Canadian registered charity that empowers the lymphoma community through education, support, advocacy, and research. Based out of Toronto (ON), we collaborate with patients, caregivers, healthcare professionals, and other organizations and stakeholders, to promote early detection, find new and better treatments for lymphoma patients, help patients access those treatments, learn about the causes of lymphoma, and work together to find a cure. Resources are provided in both English and French. For more information about our organization, please visit us at www.lymphoma.ca

Information about the Canadian Organization for Rare Disorders (CORD) can be found at https://www.raredisorders.ca/. Information about the Waldenstrom Macroglobulinemia Foundation of Canada (WMFC) can be found at https://www.wmfc.ca/.

## 2. Information Gathering

Lymphoma Canada (LC), in collaboration with CORD and WMFC, conducted an anonymous online survey for Waldenstrom Macroglobulinemia (WM) patients between February 28, 2021 – May 10, 2021. Links to the surveys were sent via e-mail to patients registered through the LC, CORD and WMFC databases. The survey was also made available via social media outlets, including Twitter, Instagram and Facebook accounts, and was also sent to physicians to share with their patients. The survey had a combination of multiple choice, rating and open-ended questions. Skipping logic was built into the survey so that respondents were asked questions only relevant to them. Open-ended responses to surveys that reflected the sentiment of a majority are included verbatim to provide a deeper understanding of patient perspectives.

There were 281 patients that responded to the survey, of which 87 patients were treated with the BTK inhibitor Ibrutinib and 22 were treated with Zanubrutinib. The remainder of the patients (n=171) without BTK inhibitor treatment experience (Ibrutinib or Zanubrutinib), were able to provide their experience with WM.. Of the WM patients who provided their demographic information for this survey **(see Tables 1 and 2),** 47% live in Canada, 56% are female, and 74% are ≥ 60 years-old.

| Table 1: Country of survey respondents (281 respondents) | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Respondents** | **CAN** | **USA** | **Europe** | **Australia** | **Other** | **Skipped** | **Total** |
| Patients WITHOUT BTK inhibitor experience | 100 | 17 | 4 | 0 | 3 | 48 | **172** |
| Patients WITH Ibrutinib experience | 30 | 46 | 5 | 1 | 2 | 3 | **87** |
| Patients WITH Zanubrutinib experience | 1 | 18 | 1 | 2 | 0 | 0 | **22** |

| Table 2: Gender and age of survey respondents (281 respondents) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Respondents** | **Age Range** | | | | | | | **Gender** | | | | |
| | **31-39** | **40-49** | **50-59** | **60-69** | **70-79** | **80-89** | **skipped** | **Female** | **Male** | **Prefer not to answer** | **Skipped** | **total** |
| Patients WITHOUT BTK inhibitor experience | 0 | 3 | 11 | 45 | 58 | 7 | 48 | 50 | 73 | 1 | 48 | **172** |
| Patients WITH Ibrutinib experience | 1 | 2 | 3 | 28 | 43 | 7 | 3 | 41 | 43 | 0 | 3 | **87** |
| Patients WITH Zanubrutinib experience | 0 | 0 | 1 | 7 | 9 | 5 | 0 | 15 | 7 | 0 | 0 | **22** |

## 3. Disease Experience

As a rare disease, not only can diagnosis of WM be difficult, but finding relevant information about WM at diagnosis can also be a challenge. Though the majority of patients (60%; n=281) did receive their WM diagnosis in less than 3 months from initial symptom presentation with their general practitioner, the remainder of patients had to wait longer; 21% of patients waited between 6-12 months and 19% waited over a year to receive a diagnosis, 11% of whom waited over 2 years. As one patient described: *"I went through multiple tests, colonoscopy, and multiple specialists before I was diagnosed. Took several months to wait for appointments with specialists too."*

WM symptoms that most impacted patients' quality of life at diagnosis (281 respondents) included fatigue (66%), drenching night sweats (28%), numbness in hands/feet (neuropathy) (24%), weight loss/loss of appetite (20%), and easy bruising/bleeding (20%). At diagnosis, respondents were asked which aspects of their life, including psychological and social impacts, were NEGATIVELY affected by their WM symptoms and diagnosis. The majority of respondents (81%) had one or more of the following impacts due to their WM symptoms and diagnosis **(Table 3).**

| Table 3: Impact of WM on patients' mental health and emotional well-being (281 respondents) | | |
|---|---|---|
| | **# of respondents** | **% of respondents** |
| Stress/Anxiety/Worry | 184 | 66% |
| Difficulty sleeping | 83 | 30% |
| Inability to take part in daily activities/routine | 79 | 28% |
| Memory loss or Problems concentrating | 54 | 19% |
| Depression | 52 | 19% |

Patients were then asked about their current symptoms and impacts to their quality of life and wellbeing, as a change in disease and its impacts may have occurred since diagnosis. Similar symptom profiles and psychological/social impacts were observed between diagnosis and current, indicating consistency of impacts to patients. Patient were then asked to currently rate on a scale of 1 to 5 (1= No impact,

5=Significant negative impact), how their WM had negatively affected various aspects of their life. Work/School/Volunteer (3.62) and Travel (3.04) were most negatively impacted by their WM (272 respondents).

## 4. Experiences With Currently Available Treatments

247 respondents provided information about their experience with WM treatments, of whom 13% were still in Watch & Wait since diagnosis and did not require treatment. 40% (n=247) were currently receiving treatment at the time of the survey, of whom 17% were receiving frontline treatment. 41% were in remission following previous line of treatment, and 6% relapsed following previous treatment and were waiting to begin treatment. The most common treatment included chemotherapy monotherapy (55%), monoclonal antibodies (63%), and BTK inhibitors (36%). When broken down, patients received the top treatments within each of the following treatment settings **(Table 4).** In the later lines of therapy, BTK inhibitors were the top treatment choice.

**Table 4: Treatments for WM Patients throughout Clinical Course (216 respondents)**

| Frontline (n) | Second Line (n) | Third Line (n) | Fourth Line (n) | Fifth Line + (n) |
|---|---|---|---|---|
| Chemotherapy monotherapy (100) | Monoclonal Antibody (31) | BTK inhibitor (19) | BTK inhibitor (11) | BTK inhibitor (8) |
| Monoclonal Antibody (91) | BTK inhibitor (20) | Monoclonal Antibody (12) | Chemotherapy monotherapy (3) | Stem-Cell Transplant (4) |
| Targeted Therapy Combination (33) | Chemotherapy monotherapy (17) | Targeted Therapy Combination (6) | Targeted Therapy Combination (3) | Targeted Therapy Combination (2) |
| Plasma Exchange (31) | Targeted Therapy Combination (16) | Proteosome Inhibitor (6) | Clinical Trial Therapy (3) | Clinical Trial Therapy (2) |
| Chemotherapy combination (26) | Chemotherapy combination (11) | Chemotherapy monotherapy (5) | - | - |

**Side effects of current treatments**: The most common side effects experienced by patients during their WM treatments are listed in **Table 5.**

**Table 5: Side effects from treatment (247 respondents)**

| Side effect (n) | % of resp. | Side effect (n) | % of resp. | Side effect (n) | % of resp. |
|---|---|---|---|---|---|
| Fatigue (178) | 72% | Peripheral neuropathy (92) | 37% | Mouth sores (53) | 22% |
| Low White Blood Cells (Neutropenia) (116) | 47% | Low platelets (thrombocytopenia) (74) | 30% | Diarrhea (50) | 20% |
| Nausea (95) | 39% | Skin rashes/severe itching (63) | 26% | Headache (47) | 19% |
| Low Red Blood Cells (anemia) (92) | 37% | Back pain or joint pain (57) | 23% | Hair loss (43) | 17% |

For these side effects, many to all were difficult to handle for patients, however 20 of 170 patients confirmed certain side effects including infections/fever (6), infusion related reactions (4), neutropenia (3), cardiac complications (2) and pneumonitis (2) among others, were the most difficult to tolerate as it resulted in hospitalization for management. None of these side effects and hospitalizations were a result from BTK inhibitors. The majority of respondents did indicate that treatment-related fatigue was one of the more challenging side effects: *" Anemia and fatigue continue to be the most challenging; recurring infection or susceptibility to infection is also a constant worry."*

The top side effects experienced longer than two years, or appeared more than two years after treatment included fatigue (36%), peripheral neuropathy (27%), and "chemo-brain" (21%) (247 respondents). There were no long-term side effects reported by respondents related to BTK inhibitors.

**Impact of treatments on quality of life:** When asked about the impact of various aspects of treatment on daily living (on a scale of 1 – 5, where 1= No impact and 5 = Significant negative impact), patients noted significant negative impacts (rating of 4-5) relating to infusion-related reactions/inabilityto tolerate treatment (19%), treatment-related fatigue (30%), and side effects from treatment (27%). Previous treatments and side effects further negatively impacted (rating 4-5) patients in their work/school/ volunteer (25%), continuing with daily activities (22%), and travel (27%) (247 respondents). In comparison (reported under section 6), BTK inhibitors did not negatively impact patient's mental health, work/school/volunteer, family/friends, intimate relationships, ability to continue with daily activities and personal image, and actually had a positive impact in each of these categories.

The majority of patients were able to access treatment locally (78%; 244 respondents), and those that could not specified reasons including living in a community without a cancer centre (9%) and treatment not being available at their local cancer centre (4%). As a result of not being able to access treatment locally, this impacted patients by increasing their worry over prognosis/survival (16%), required long and exhaustive trips to access treatment (13%) and impacted daily activities (13%) (122 respondents). These impacts are greater for the patients that have to stay at or close to the treatment centre for up to and more than a month (11%; 244 respondents). With treatments such as oral BTK inhibitors that do not involve travelling to a hospital or centre for administration, this can limit the aforementioned negative impacts regarding treatment access. Additional financial impacts are also important considerations for WM patients including cost of medications (67%), parking (26%), and travel (21%) (244 respondents). As reported by one patient: *"During the treatment, I spent several hours two days a week getting therapy and then a couple of days to recover significantly which affected my available time for other things. When the protocol changed allowing my treatment to be given as an injection instead of IV, it cut down on the time which helped."*

## 5. Improved Outcomes

Patients were asked whether there were enough treatment options available to them to manage/treat their WM. On a scale of 1 to 10 (1=not important, 10 = very important), patients rated having a choice in their treatment (8.47) and having enough treatment options available (8.38) were very important to them (238 respondents). As stated by one patient: *"The median survival time in 1990s when I was diagnosed was only 5 years. That number has more than doubled as a consequence of new treatments. I am confident that a treatment that cures this cancer will be forthcoming within the next 10 years."*

**Patient preferences:** Respondents were asked to rate, on a scale of 1 to 5 (1 = not important; 5 = extremely important), important considerations for new treatments for WM. "Longer survival" and "longer remission" were rated as the most important outcomes for a new therapy **(Table 6).**

**Table 6: Treatment preferences (238 respondents)**

| Treatment outcome or factor | Rating = 5 (Extremely important) | Weighted average |
|---|---|---|
| Longer survival | 75% | 4.64 |
| Better quality of life | 70% | 4.58 |
| Longer Remission | 76% | 4.68 |

| | | |
|---|---|---|
| Fewer side effects | 57% | 4.28 |

To access new treatments for their WM, 67% of patients reported they would be interested in participating in a clinical trial (238 respondents).

Patients were more likely to accept known risks/side effects for a new treatment related to side effects that were not life-threatening ; very few patients were willing to tolerate severe and long-term side effects (238 respondents). On a scale of 1 to 5 (1=less important to control, 5=most important to control), patients rated headache/cognitive changes (56%), changes in vision (58%), shortness of breath (46%), abdominal discomfort (nausea/vomiting/diarrhea/constipation) (42%) and fatigue (42%), as the most important symptoms for new WM treatments to control (238 respondents). As described in section 6, BTK inhibitors control many of these symptoms. Patients listed their expectations for new treatment options:

*" A targeted oral treatment that will not cause secondary cancers or more discomfort than the disease itself."*

*"Provide increase in quality of life and longevity with minimal side effects"*

## 6. Experience With Drug Under Review

Patient experience for both BTK inhibitors, Ibrutinib and Zanubrutinib, was collected through this survey. As a comparator BTK inhibitor, patient experience with Ibrutinib was collected Summary results of the comparator trial was shared with respondents, highlighting Zanubrutinib's similar response rates (progression-free survival, complete response) with Ibrutinib, and reduced side effect profile. Based on this information and treatment experience, 45% of patients elected they would use Zanubrutinib over other BTK inhibitors, while 12% would use Zanubrutinib after treatment with another BTK inhibitor has failed; 43% were unsure (231 respondents). Reasons for choosing Zanubrutinib over other BTK inhibitors included less side effects (63%)and a slightly better response rate (even if not statistically significant) compared to other BTK inhibitors (34%) (231 respondents). 62% of patients would also choose Zanubrutinib if it was recommended by their doctor.

**Experience with Ibrutinib**

37% of patients received treatment with ibrutinib (237 respondents), and were able to access it through options including private insurance (32%), compassionate access programs (28%), and clinical trials (12%) among other options (87 respondents). 62% of patients were still taking the treatment at the time of completing the survey, while the remaining patients had to stop treatment because they either completed all required treatment cycles (13%), their disease progressed on treatment (9%), or they could not tolerate the side effects (14%), among other reasons (87 respondents).

Patients were asked about WM symptom management with Ibrutinib. 22% of patients found that all of their WM symptoms were managed with Ibrutinib, while 17% of patients did not have any of their symptoms managed by this treatment (87 respondents). Patients provided further clarity as to the specific symptoms that Ibrutinib managed and controlled for them which included fatigue (45%), night sweats (30%), weight loss (22%), and enlarged lymph nodes/abdomen (18%) (87 respondents). However, there were Ibrutinib-related treatment side effects which included easy bruising/bleeding (39%), fatigue (24%), skin rashes/itching (24%), low platelets (thrombocytopenia) (22%), and irregular heart beat/cardiac issues (21%).

When asked about which aspects of a patients life were affected by Ibrutinib treatment and side effects, patients rated on a scale of 1 to 5 (1=significant **negative** impact, 3= no impact, 5= significant **positive**

impact) that Ibrutinib did not negatively impact their mental health, travel, personal image, intimate relationships and family/friendships, and had an inclination to positively impact their ability to continue with work/school/volunteer (3.71) with daily activities (3.65).

**Overall Experience and Recommendation - Ibrutinib Therapy:** When asked to describe their experience with Ibrutinib, 80% of patients responded they had a good to excellent experience with the therapy, and 72% of patients mentioned they would take this treatment option again if available to them. 80% of patients would recommend this as a treatment option for other WM patients. Patients further commented:

*"For me, it was life-changing. I would hope others might have the same experience."*
*"I feel far better now than I ever did under a chemo regime - the difference is extreme."*
*"Its effectiveness in managing symptoms, ease of taking it (daily capsules at home) and minimal side effects for me."*

## Experience with Zanubrutinib

Between 2016-2021, 22 patients received treatment with Zanubrutinib. Patients largely accessed this treatment a clinical trial (50%) or through private insurance (27%), while 3% were able to access it through compassionate access program from the drug manufacturer; 2% detailed other. At the time of survey completion, 91% of respondents were still taking the treatment; 1 patient stopped to switch to another treatment and go back to Zanubrutinib, while another patient stopped due to unrelated infection (22 respondents). Patients provided their treatment history prior to receiving Zanubrutinib; 7 patients received Zanubrutinib as frontline treatment, 7 received it in the second-line setting, 2 received it as a third-line treatment, and 6 patients received it as a fourth-line or greater treatment (22 respondents). The most common therapies received prior to Zanubrutinib treatment included chemotherapy and monoclonal antibodies.

Patients were asked about WM symptom management with Zanubrutinib. 27% of patients found that all of their WM symptoms were managed with Zanubrutinib, while 9% of patients did not have any of their symptoms managed by this treatment (22 respondents). Patients provided further clarity to the specific symptoms that Zanubrutinib managed and controlled for which included fatigue (68%), night sweats (32%), shortness of breath (27%) and enlarged lymph nodes/abdomen (23%) (22 respondents). Neuropathy was the WM symptom that was least managed by Zanubrutinib.

**Side Effects:** There were no patients that had to stop this Zanubrutinib due to treatment-related side effects. 13% of patients did not experience any side effects. Of those that did report side effects, the most common included easy bruising/bleeding (55%), diarrhea (18%), neutropenia (18%), skin rash/itching (8%), muscle/joint pain (18%), and muscle spasms (18%) (22 respondents). The most difficult to tolerate side effects included diarrhea, bruising, and itching/skin rash. No patients were admitted to the hospital to treat any of these side effects. As reported by two patients:

*"I like that it is an oral drug and that it has not produced any noticeable side effects."*
*"It feels a bit like a miracle drug since my condition changed so rapidly once I started taking it. And the side effects have been minimal."*

**Quality of Life:** 22 respondents provided details on whether their quality of life was affected by various aspects of the treatment, rating this impact on a scale of 1 (no negative impact) to 5 (significant negative impact). None of the weighted averages for these responses was higher than 2, suggesting that Zanubrutinib did not have a significant negative impact on patients' quality-of-life **(Table 7).**

**Table 7: Impact of Zanubrutinib therapy on patients Quality of Life (22 respondents)**

| Aspect of Zanubrutinib therapy | Weighted average | Rating 1-2 (Minimal Negative Impact (%) | Rating 4-5 (Significant Negative Impact) (%) |
|---|---|---|---|
| Number of Clinic Visits Required | 1.45 | 82% | 0% |
| Length/Frequency of Taking Drug | 1.67 | 69% | 10% |
| Short-Term Side Effects | 1.83 | 59% | 5% |
| Long-Term/Late Side Effects | 1.6 | 59% | 5% |

When asked about which aspects of a patients life were affected by Zanubrutinib treatment and side effects, patients rated on a scale of 1 to 5 (1=significant **negative** impact, 3= no impact, 5= significant **positive** impact). The majority of patients rated that Zanubrutinib did not impact their work/school, travel, mental health, personal image, intimate relationships and family/friendships, but did have an inclination to positively impact their ability to continue with daily activities (weighted average 3.74).

**Overall Experience and Recommendation Zanubrutinib Therapy:** In comparison to patients that received other treatments, patients noted that Zanubrutinib had less side effects (64%), did not impact quality of life to the same extent as past treatments (36%), and had a better and faster response rate (41%) compared to previous treatments (22 respondents). When asked to describe their experience with Zanubrutinib, 95% of patients responded they had a good to excellent experience with the therapy, with the remaining patient having a satisfactory experience (22 respondents). 95% of patients mentioned they would take this treatment option again if available and recommended by their doctor, and would also recommend it to other WM patients; 1 was unsure (22 respondents). Patients further commented:

*"I am grateful for the opportunity to participate in a clinical trial for a drug that is less toxic than ibrutinib and that gives me such a deep response."*
*"It amazes me that people choose infusion therapy over the ease of Zanubrutinib."*
From one patient who couldn't participate in accessing Zanubrutinib, commented:
*"We are hearing and seeing on-line that our friends on Zanubrutinib trial are vibrant, active, able to work, etc. No side effects - except brief adjustments. That would be a wonderful opportunity to access!"*

**Comparison of Ibrutinib to Zanubrutinib:** There were six patients that were treated with both Zanubrutinib and Ibrutinib. A comparison on patient experience was assessed between the two BTK inhibitors **(Table 8).** Overall patients treated with both BTK inhibitors preferred their experience with Zanubrutinib compared to Ibrutinib, citing less impactful side effects.

**Table 9: Comparison of Patient Experience with Ibrutinib versus Zanubrutinib therapy (6 respondents)**

| | Ibrutinib | | | | | Zanubrutinib | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| # | Reason for stop | WM Symptoms Managed | Side Effects | Take again ? | Experience | Reason for stop | WM Symptoms Managed | Side Effects | Take again ? | Experience | Comparing treatment | Patient Comments |
| 1 | stopped ; side effects | Fatigue, Enlarged LN, Fever/Chills, Night Sweats | Nausea/ vomiting, Diarrhea, Easy Bruising/ Bleeding | no | satisfactory | still receiving | fatigue, enlarged LN, fever/chills, night sweats, managed all symptoms | diarrhea, easy bruising/ bleeding | Yes | Very good | 1,2,3,4 | *Zanubrutinib is as effective as ibrutinib but fewer / less severe side effects* |
| 2 | stopped ; side effects | did not manage any symptoms | Nausea/ vomiting, severe diarrhea | no | poor | still receiving | fatigue | diarrhea, easy bruising/ | yes | very good | 1,4 | *With Zanubrutinib, blood levels are within normal limits for the first time* |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | bleeding, muscle spasms | | | | *since before diagnoses.* |
| 3 | stopped; side effects | Fatigue, fever/chills, frequent infections, night sweats, shortness of breath | mouth sores, cough, irregular heart beat/heart problems, easy bruising/ bleeding, hypertension | No | Good | still receiving | fatigue, frequent infections, fever/chills, night sweats, shortness of breath | mouth sores, easy bruising/ bleeding | Yes | Excellent | 1,2,4 | *Zanubrutinib works quickly* |
| 4 | Stopped; prefer Zanubrutinib | managed all symptoms | hair loss | I'm not sure | satisfactory | still receiving | fatigue, headaches/ cognitive changes | easy bruising/ bleeding | Yes | very good | 1,2,4 | *Zanubrutinib has fewer side effects and better efficacy* |
| 5 | stopped; side effects | fatigue, neuropathy, sensitivity to cold | fatigue, neuropathy, easy bruising/ bleeding | I'm not sure | Very good | still receiving | neuropathy, managed all symptoms | diarrhea, neuropathy | Yes | very good | 1 | *did well on Ibrutinib until side effects* |
| 6 | stopped; side effects | fatigue, shortness of breath, neuropathy | fatigue, irregular heart beat/heart problems, shortness of breath | No | Poor | still receiving | neuropathy, shortness of breath | easy bruising/ bleeding | Yes | Very good | 1 | *Other than minimal side effects, I have been satisfied with results from Zanubrutinib.* |

1= Less side effects compared to previous treatments; 2=faster and better response rate compared to previous treatments; 3=I had to take Zanubrutinib for a longer amount of time then the length of past treatments, 4=Zanubrutinib negatively impacted my quality of life less then past treatments

7. **Companion Diagnostic Test** **There is no companion diagnostic testing**
8. **Anything Else?** N/A

## 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. **N/A**
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. **N/A**
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. **N/A**

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: Kaitlyn Beyfuss-Laski; Position: Manager of Patient Programs, Research & Advocacy; Patient Group: Lymphoma Canada; Date: 12-May-2021